Request. Paul Schulwitz

Access DB# 136040

SEARCH REQUEST FORM

RECEIVED
OCT 25 2004
Scientific and Technical Information Center

Requester's Full Name: Sabiha Qazi Examiner #: 74141 Date: 10/25/04
Art Unit: 1616 Phone Number: 20622 Serial Number: 10/720,487
Mail Box and Bldg/Room Location: 4C70 Rem. 4A45 Results Format Preferred (circle): PAPER DISK E-MAIL
If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Pharmaceutical Prep - - - -

Inventors (please provide full names): Ludwig Wild et al

Earliest Priority Filing Date: ~~4/15/03~~ 6/26/2001

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search for the methods of use of estra 1, 3, 5 (10) - triene-3 17β-diol-17- Valerate, as in cla 1-9.

Please see attached sheet

Thank You

STAFF USE ONLY

Searcher: _____
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 10/28
Searcher Prep & Review Time: 20
Clerical Prep Time: _____
Online Time: 18

PTO-1590 (8-01)

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) 1
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN 292.43
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

```
=> fil reg; d ide
FILE 'REGISTRY' ENTERED AT 10:45:36 ON 02 MAR 2006
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STRUCTURE FILE UPDATES:    1 MAR 2006  HIGHEST RN 875609-25-9
DICTIONARY FILE UPDATES:   1 MAR 2006  HIGHEST RN 875609-25-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

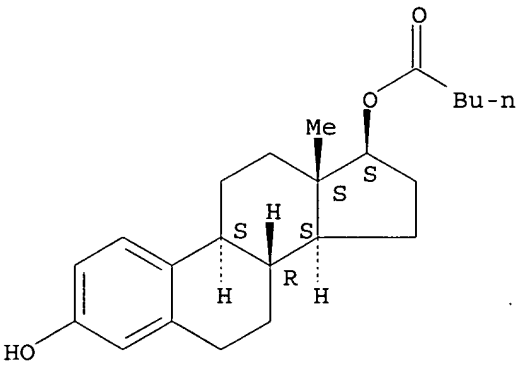
REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html


L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   979-32-8 REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI)  (CA
     INDEX NAME)
OTHER CA INDEX NAMES:
CN   Estradiol valerate (6CI)
CN   Estradiol, 17-valerate (7CI, 8CI)
OTHER NAMES:
CN   3-Hydroxy-17β-valeroyloxyestra-1,3,5(10)-triene
CN   Atladiol
CN   Climaval
CN   Deladiol
CN   Delahormone unimatic
CN   Delestrogen
CN   Delestrogen 4x
CN   Dura-Estradiol
CN   Estra-1,3,5(10)-triene-3,17β-diol 17-valerate
CN   Estradiol 17β-valerate
CN   Estradiol valerianate
```

CN Estraval
CN Femogex
CN Gynogen LA
CN Gynogen LA 40
CN Gynokadin
CN Neofollin
CN NSC 17590
CN Nuvelle
CN Oestradiol valerinate
CN Pelanin Depot
CN Pharlon
CN Primofol-Depot
CN Primogyn-Depot
CN Progynon-Depot
CN Progynova
CN Valergen
FS STEREOSEARCH
DR 907-12-0, 69557-95-5
MF C23 H32 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PATDPASPC, PROMT, PS, RTECS*, SCISEARCH, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

916 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
920 REFERENCES IN FILE CAPLUS (1907 TO DATE)
39 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> => d ide

L15 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN **9034-40-6** REGISTRY
ED Entered STN: 16 Nov 1984

Searched by Barb O'Bryen, STIC 2-2518

CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Fertiral
CN GnRH
CN GonaCon/AdjuVac
CN Gonadoliberin
CN Gonadotropin-releasing factor
CN Gonadotropin-releasing hormone
CN Gonadotropin-releasing peptide
CN Kryptocur
CN LH-releasing factor
CN LH-releasing hormone
CN LH-RF
CN LH-RH
CN LRF
CN LRH
CN Luliberin
CN Luteinizing hormone-releasing hormone
CN Luteostimulin
CN Nialutin
CN Relefact LH-RH
CN Reproboost
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CHEMCATS, CHEMLIST, CIN, CSCHEM, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MRCK*, NIOSHTIC, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16339 REFERENCES IN FILE CA (1907 TO DATE)
1488 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16360 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> =>

```
=> fil reg; d stat que l12
FILE 'REGISTRY' ENTERED AT 12:08:13 ON 02 MAR 2006
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STRUCTURE FILE UPDATES:    1 MAR 2006  HIGHEST RN 875609-25-9
DICTIONARY FILE UPDATES:   1 MAR 2006  HIGHEST RN 875609-25-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

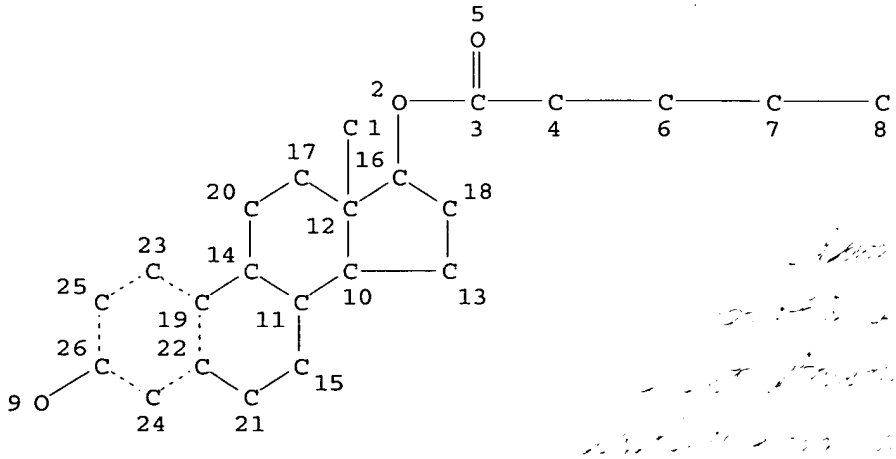
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html


L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
```



Searched by Barb O'Bryen, STIC 2-2518

```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  26

STEREO ATTRIBUTES: NONE
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11


=> fil capl; d que nos l18; d que nos l30

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FILE COVERS 1907 - 2 Mar 2006  VOL 144 ISS 10
FILE LAST UPDATED: 1 Mar 2006  (20060301/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L14         1074 SEA FILE=CAPLUS ABB=ON  L12
L15            1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L16        16360 SEA FILE=CAPLUS ABB=ON  L15
L17          209 SEA FILE=CAPLUS ABB=ON  L16(L)ADV/RL - Role ADV = adverse effect
L18            1 SEA FILE=CAPLUS ABB=ON  L17 AND L14
```

```
L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L14         1074 SEA FILE=CAPLUS ABB=ON  L12
L15            1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L16        16360 SEA FILE=CAPLUS ABB=ON  L15
L21          499 SEA FILE=CAPLUS ABB=ON  RETENTION/OBI(L)FLUID#/OBI
L22          661 SEA FILE=CAPLUS ABB=ON  HOT/OBI(L)FL!SH?/OBI
L23         5507 SEA FILE=CAPLUS ABB=ON  HEADACHE#/OBI
L24         2103 SEA FILE=CAPLUS ABB=ON  NAUSEA/OBI
L25        11069 SEA FILE=CAPLUS ABB=ON  DEPRESSION/OBI(L)MENTAL/OBI
L26           40 SEA FILE=CAPLUS ABB=ON  (MAMMARY/OBI OR BREAST#/OBI)(L)TENDER?/
                 OBI
L27        50049 SEA FILE=CAPLUS ABB=ON  CARDIOVASCULAR/OBI
L28          294 SEA FILE=CAPLUS ABB=ON  GYNECOMASTI?/OBI
L29           56 SEA FILE=CAPLUS ABB=ON  PROSTAT?/OBI(L)ENLARG?/OBI
L30            3 SEA FILE=CAPLUS ABB=ON  L16 AND L14 AND (L21 OR L22 OR L23 OR
                 L24 OR L25 OR L26 OR L27 OR L28 OR L29)


=> s l18 or l30

L166           3 L18 OR L30

=> fil toxcenter; d que nos l37

FILE 'TOXCENTER' ENTERED AT 12:08:16 ON 02 MAR 2006
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FILE COVERS 1907 TO 28 Feb 2006 (20060228/ED)

This file contains CAS Registry Numbers for easy and accurate substance
identification.

The MEDLINE file segment has been updated with 2006 MEDLINE data and
features.  See HELP RLOAD for details.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2006 vocabulary.
See http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html
for a description of changes.


L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
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L15           1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L35         558 SEA FILE=TOXCENTER ABB=ON  L12
L36        3200 SEA FILE=TOXCENTER ABB=ON  L15
L37           7 SEA FILE=TOXCENTER ABB=ON  L35 AND L36


=> fil biosis; d que nos l66

FILE 'BIOSIS' ENTERED AT 12:08:17 ON 02 MAR 2006
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 1 March 2006 (20060301/ED)



L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15           1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L50        1002 SEA FILE=BIOSIS ABB=ON  L12
L51       13923 SEA FILE=BIOSIS ABB=ON  L15
L53        1583 SEA FILE=BIOSIS ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L54        1296 SEA FILE=BIOSIS ABB=ON  HOT FL!SH?
L55       24834 SEA FILE=BIOSIS ABB=ON  HEADACHE#
L56       20197 SEA FILE=BIOSIS ABB=ON  NAUSEA
L57      119520 SEA FILE=BIOSIS ABB=ON  DEPRESSION
L58         262 SEA FILE=BIOSIS ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L59     1807338 SEA FILE=BIOSIS ABB=ON  CARDIOVASCULAR
L60        1659 SEA FILE=BIOSIS ABB=ON  GYNECOMASTI?
L61         652 SEA FILE=BIOSIS ABB=ON  PROSTAT?(2A)ENLARG?
L62      185953 SEA FILE=BIOSIS ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR
                EVENT?)
L65       21420 SEA FILE=BIOSIS ABB=ON  (LUTEINIZING OR GONADOTROPIN)(1W)RELEAS
                ING HORMONE#
L66           3 SEA FILE=BIOSIS ABB=ON  L50 AND (L51 OR L65) AND (L53 OR L54
                OR L55 OR L56 OR L57 OR L58 OR L59 OR L60 OR L61 OR L62)


=> fil uspatf; d que nos l69

FILE 'USPATFULL' ENTERED AT 12:08:18 ON 02 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Feb 2006 (20060228/PD)
FILE LAST UPDATED: 28 Feb 2006 (20060228/ED)
HIGHEST GRANTED PATENT NUMBER: US7007305
HIGHEST APPLICATION PUBLICATION NUMBER: US2006041984
CA INDEXING IS CURRENT THROUGH 28 Feb 2006 (20060228/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Feb 2006 (20060228/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005
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L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15            1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L67          117 SEA FILE=USPATFULL ABB=ON  L12
L68         1036 SEA FILE=USPATFULL ABB=ON  L15
L69            5 SEA FILE=USPATFULL ABB=ON  L67 AND L68
```

```
=> fil embase; d que nos l75 ; d que nos l78

FILE 'EMBASE' ENTERED AT 12:08:19 ON 02 MAR 2006
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 FILE COVERS 1974 TO 24 Feb 2006 (20060224/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

```
L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L70         2369 SEA FILE=EMBASE ABB=ON  L12
L71         2157 SEA FILE=EMBASE ABB=ON  ESTRADIOL VALERATE/CT
L72        20312 SEA FILE=EMBASE ABB=ON  GONADORELIN/CT
L74          197 SEA FILE=EMBASE ABB=ON  L72(L)AE/CT
L75            1 SEA FILE=EMBASE ABB=ON  L74 AND (L70 OR L71)
```

```
L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L70         2369 SEA FILE=EMBASE ABB=ON  L12
L71         2157 SEA FILE=EMBASE ABB=ON  ESTRADIOL VALERATE/CT
L72        20312 SEA FILE=EMBASE ABB=ON  GONADORELIN/CT
L73           67 SEA FILE=EMBASE ABB=ON  (L70 OR L71) AND L72
L77       363126 SEA FILE=EMBASE ABB=ON  SIDE EFFECT/CT
L78            5 SEA FILE=EMBASE ABB=ON  L73 AND L77
```

```
=> s l75 or l78

L167             5 L75 OR L78

=> fil biotechno; d que nos l94

FILE 'BIOTECHNO' ENTERED AT 12:08:20 ON 02 MAR 2006
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FILE LAST UPDATED: 7 JAN 2004       <20040107/UP>
FILE COVERS 1980 TO 2003.

>>>  BIOTECHNO IS NO LONGER BEING UPDATED AS OF 2004  <<<

>>>  SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN
     /CT AND BASIC INDEX  <<<


L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15           1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L79         357 SEA FILE=BIOTECHNO ABB=ON  L12
L80         385 SEA FILE=BIOTECHNO ABB=ON  ESTRADIOL VALERATE
L81        5768 SEA FILE=BIOTECHNO ABB=ON  L15
L82        9488 SEA FILE=BIOTECHNO ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                GONADOTROPIN)(1W)RELEASING(W)(FACTOR# OR  HORMONE#))
L83          48 SEA FILE=BIOTECHNO ABB=ON  (L79 OR L80) AND (L81 OR L82)
L84         279 SEA FILE=BIOTECHNO ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L85         287 SEA FILE=BIOTECHNO ABB=ON  HOT FL!SH?
L86        2536 SEA FILE=BIOTECHNO ABB=ON  HEADACHE#
L87        3002 SEA FILE=BIOTECHNO ABB=ON  NAUSEA
L88        5916 SEA FILE=BIOTECHNO ABB=ON  DEPRESSION
L89          17 SEA FILE=BIOTECHNO ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L90        9915 SEA FILE=BIOTECHNO ABB=ON  CARDIOVASCULAR
L91         187 SEA FILE=BIOTECHNO ABB=ON  GYNECOMASTI?
L92          43 SEA FILE=BIOTECHNO ABB=ON  PROSTAT?(2A)ENLARG?
L93       14495 SEA FILE=BIOTECHNO ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR
                EVENT?)
L94           5 SEA FILE=BIOTECHNO ABB=ON  L83 AND (L84 OR L85 OR L86 OR L87
                OR L88 OR L89 OR L90 OR L91 OR L92 OR L93)


=> fil agricola; d que nos l116;d que nos l119

FILE 'AGRICOLA' ENTERED AT 12:08:23 ON 02 MAR 2006


FILE COVERS 1970 TO 7 Feb 2006 (20060207/ED)

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```
L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15           1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L101        111 SEA FILE=AGRICOLA ABB=ON  L12
L102         60 SEA FILE=AGRICOLA ABB=ON  ESTRADIOL VALERATE
L103       1744 SEA FILE=AGRICOLA ABB=ON  L15
L104       1358 SEA FILE=AGRICOLA ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                GONADOTROPIN)(1W)RELEASING(W)(FACTOR# OR  HORMONE#))
L105          7 SEA FILE=AGRICOLA ABB=ON  (L101 OR L102) AND (L103 OR L104)
L106         53 SEA FILE=AGRICOLA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L107         16 SEA FILE=AGRICOLA ABB=ON  HOT FL!SH?
L108        206 SEA FILE=AGRICOLA ABB=ON  HEADACHE#
L109        221 SEA FILE=AGRICOLA ABB=ON  NAUSEA
L110       3636 SEA FILE=AGRICOLA ABB=ON  DEPRESSION
L111         36 SEA FILE=AGRICOLA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L112       6079 SEA FILE=AGRICOLA ABB=ON  CARDIOVASCULAR
L113          5 SEA FILE=AGRICOLA ABB=ON  GYNECOMASTI?
L114          5 SEA FILE=AGRICOLA ABB=ON  PROSTAT?(2A)ENLARG?
L115       7300 SEA FILE=AGRICOLA ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR
                EVENT?)
L116          0 SEA FILE=AGRICOLA ABB=ON  L105 AND (L106 OR L107 OR L108 OR
                L109 OR L110 OR L111 OR L112 OR L113 OR L114 OR L115)



L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15           1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L101        111 SEA FILE=AGRICOLA ABB=ON  L12
L102         60 SEA FILE=AGRICOLA ABB=ON  ESTRADIOL VALERATE
L103       1744 SEA FILE=AGRICOLA ABB=ON  L15
L104       1358 SEA FILE=AGRICOLA ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                GONADOTROPIN)(1W)RELEASING(W)(FACTOR# OR  HORMONE#))
L105          7 SEA FILE=AGRICOLA ABB=ON  (L101 OR L102) AND (L103 OR L104)
L117       7071 SEA FILE=AGRICOLA ABB=ON  MAN/CT
L118      10394 SEA FILE=AGRICOLA ABB=ON  WOMEN/CT
L119          0 SEA FILE=AGRICOLA ABB=ON  L105 AND (L117 OR L118)


=> fil drugu; d que nos l135; d que nos l146

FILE 'DRUGU' ENTERED AT 12:08:24 ON 02 MAR 2006
```

FILE LAST UPDATED: 1 MAR 2006 <20060301/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

```
L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L120        371 SEA FILE=DRUGU ABB=ON  L12
L123       2266 SEA FILE=DRUGU ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                GONADOTROPIN)(1W)RELEASING(W)(FACTOR# OR  HORMONE#))
L125        765 SEA FILE=DRUGU ABB=ON  ESTRADIOL-VALERATE/CT
L127       8458 SEA FILE=DRUGU ABB=ON  RELEASING-FACTOR#/CT
L130         10 SEA FILE=DRUGU ABB=ON  (L120 OR L125) AND L127 AND L123
L131     311308 SEA FILE=DRUGU ABB=ON  AE = adverse effect
L134     240306 SEA FILE=DRUGU ABB=ON  ADVERSE REACTIONS/CC
L135          6 SEA FILE=DRUGU ABB=ON  L130 AND (L131 OR L134)
```

```
L2            1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3              STR
L5           29 SEA FILE=REGISTRY FAM FUL L3
L6              SEL  L2 1- RN :       1 TERM
L7           25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9            4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11           2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12          27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L120        371 SEA FILE=DRUGU ABB=ON  L12
L123       2266 SEA FILE=DRUGU ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                GONADOTROPIN)(1W)RELEASING(W)(FACTOR# OR  HORMONE#))
L125        765 SEA FILE=DRUGU ABB=ON  ESTRADIOL-VALERATE/CT
L127       8458 SEA FILE=DRUGU ABB=ON  RELEASING-FACTOR#/CT
L130         10 SEA FILE=DRUGU ABB=ON  (L120 OR L125) AND L127 AND L123
L136       6084 SEA FILE=DRUGU ABB=ON  FLUSHING/CT
L137      24956 SEA FILE=DRUGU ABB=ON  HEADACHE/CT
L138      42819 SEA FILE=DRUGU ABB=ON  NAUSEA/CT
L139      15233 SEA FILE=DRUGU ABB=ON  DEPRESSION/CT
L140       3693 SEA FILE=DRUGU ABB=ON  WEIGHT GAIN/CT
L141        606 SEA FILE=DRUGU ABB=ON  GYNECOMASTIA/CT
L142        676 SEA FILE=DRUGU ABB=ON  PROSTATE-HYPERPLASIA/CT OR PROSTATE-HYPE
                RTROPHY/CT
L143        582 SEA FILE=DRUGU ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L144       1427 SEA FILE=DRUGU ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L145      23742 SEA FILE=DRUGU ABB=ON  CARDIOVASCULAR
L146          5 SEA FILE=DRUGU ABB=ON  L130 AND (L136 OR L137 OR L138 OR L139
                OR L140 OR L141 OR L142 OR L143 OR L144 OR L145)
```

=> s l135 or l146

```
L168          6 L135 OR L146

=> fil ipa; d que nos l152

FILE 'IPA' ENTERED AT 12:08:26 ON 02 MAR 2006
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FILE COVERS 1970 TO 1 MAR 2006 (20060301/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L15            1 SEA FILE=REGISTRY ABB=ON  9034-40-6
L148          71 SEA FILE=IPA ABB=ON  L12
L149          81 SEA FILE=IPA ABB=ON  ESTRADIOL VALERATE
L150           1 SEA FILE=IPA ABB=ON  L15
L151         764 SEA FILE=IPA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROP
                 IN)(1W)RELEASING(W)(HORMONE# OR FACTOR#))
L152           4 SEA FILE=IPA ABB=ON  (L148 OR L149) AND (L150 OR L151)


=> fil imsre; d que nos l157

FILE 'IMSRESEARCH' ENTERED AT 12:08:27 ON 02 MAR 2006
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FILE COVERS 1977 TO 24 Feb 2006 (20060224/ED)

 ###################################################################
 #                                                                 #
 #                    !!! ATTENTION !!!                            #
 #                                                                 #
 #  Welcome to IMSRESEARCH.  A special subscriber rate             #
 #  is available to purchasers of the IMSworld publication,        #
 #  R&D Focus, part of the Drug Intelligence range.                #
 #                                                                 #
 #  For detailed information regarding eligibility and             #
 #  authorization for this subscriber discount, please contact     #
 #  IMS HEALTH Customer Services directly by phone                 #
 #  at +44(0)20-7393-5888, or email globaldirect@uk.imshealth.com  #
 #  See HELP SUBSCRIPTION for more information.                    #
 #                                                                 #
 ###################################################################

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 The file name was changed from DRUGUPDATES to IMSRESEARCH on 7 Dec. 2003.
 The file name DRUGUPDATES is now an alias for IMSRESEARCH.
```

```
L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L153           2 SEA FILE=IMSRESEARCH ABB=ON  L12
L154          13 SEA FILE=IMSRESEARCH ABB=ON  ESTRADIOL VALERATE
L156          74 SEA FILE=IMSRESEARCH ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                 GONADOTROPIN)(1W)RELEASING(W)(HORMONE# OR FACTOR#))
L157           0 SEA FILE=IMSRESEARCH ABB=ON  (L153 OR L154) AND L156

=> fil adisin; d que nos l162

FILE 'ADISINSIGHT' ENTERED AT 12:08:28 ON 02 MAR 2006
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FILE COVERS 1998 TO 23 Feb 2006 (20060223/ED)
FILE LAST UPDATED: 23 FEB 2006 (20060223/ED)


L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L158           2 SEA FILE=ADISINSIGHT ABB=ON  L12
L159           9 SEA FILE=ADISINSIGHT ABB=ON  ESTRADIOL VALERATE
L161          64 SEA FILE=ADISINSIGHT ABB=ON  GONADORELIN OR ((LUTEINIZING OR
                 GONADOTROPIN)(1W)RELEASING(W)(HORMONE# OR FACTOR#))
L162           1 SEA FILE=ADISINSIGHT ABB=ON  (L158 OR L159) AND L161


=> fil medl; d que nos l100

FILE 'MEDLINE' ENTERED AT 12:08:29 ON 02 MAR 2006

  FILE LAST UPDATED: 1 MAR 2006 (20060301/UP).  FILE COVERS 1950 TO DATE.

  On December 11, 2005, the 2006 MeSH terms were loaded.

  The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
  on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
  See also:

     http://www.nlm.nih.gov/mesh/
     http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
     http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
     http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

  OLDMEDLINE is covered back to 1950.
```

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11
L95          655 SEA FILE=MEDLINE ABB=ON  L12
L96         4412 SEA FILE=MEDLINE ABB=ON  ESTRADIOL/CT(L)AA/CT
L97        22442 SEA FILE=MEDLINE ABB=ON  GONADORELIN+NT/CT
L99          966 SEA FILE=MEDLINE ABB=ON  L97(L)AE/CT
L100           7 SEA FILE=MEDLINE ABB=ON  L99 AND (L95 OR L96)
```

```
=> => dup rem l166,l69,l100,l168,l94,l152,l66,l167,l37,l162
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
FILE 'CAPLUS' ENTERED AT 12:10:30 ON 02 MAR 2006
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PROCESSING COMPLETED FOR L166
PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L100
PROCESSING COMPLETED FOR L168
PROCESSING COMPLETED FOR L94
```

PROCESSING COMPLETED FOR L152
PROCESSING COMPLETED FOR L66
PROCESSING COMPLETED FOR L167
PROCESSING COMPLETED FOR L37
PROCESSING COMPLETED FOR L162
L169 41 DUP REM L166 L69 L100 L168 L94 L152 L66 L167 L37 (5 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE CAPLUS
ANSWERS '4-7' FROM FILE USPATFULL
ANSWERS '8-14' FROM FILE MEDLINE
ANSWERS '15-19' FROM FILE DRUGU
ANSWERS '20-24' FROM FILE BIOTECHNO
ANSWERS '25-27' FROM FILE IPA
ANSWERS '28-30' FROM FILE BIOSIS
ANSWERS '31-35' FROM FILE EMBASE
ANSWERS '36-40' FROM FILE TOXCENTER
ANSWER '41' FROM FILE ADISINSIGHT

=> d ibib ed abs hitstr 1-7; d iall 8-41

L169 ANSWER 1 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:701801 CAPLUS
DOCUMENT NUMBER: 141:200203
TITLE: Pharmaceutical preparations containing modified estradiol or modified estriol for treating side effects during and/or after GnRHa therapy
INVENTOR(S): Oettel, Michael; Wild, Ludwig; Licht, Peter; Neuwinger, Joachim; Hummel, Wolfgang; Dittrich, Ralph
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 891,722.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

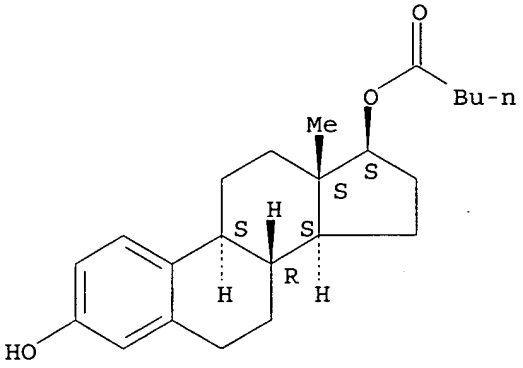
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004167111	A1	20040826	US 2003-729487		20031205
US 2002002153	A1	20020103	US 1999-291385		19990414
US 2002065260	A1	20020530	US 2001-891722		20010626
US 6689768	B2	20040210			
PRIORITY APPLN. INFO.:			US 1998-81791P	P	19980415
			US 1999-291385	B2	19990414
			US 2001-891722	A2	20010626
			DE 1998-19815060	A	19980403

ED Entered STN: 27 Aug 2004
AB The pharmaceutical prepns. for treating side effects, such as hot flashes, prostate enlargement and gynecomastia, during and/or after treatment with analogs or antagonists of gonadotropin-releasing hormone (GnRHa therapy) contain an effective amount of a chemical modified derivative of 17α-estradiol, a chemical modified derivative of 17β-estradiol and/or a chemical modified derivative of estriol. Pharmaceutical prepns. containing estra
1,3,5(10)-triene-3,17β-diol-17-valerate as the effective ingredient are particularly preferred. Hot flashes tripped by GnRHa therapy with Decapeptyl-Depot in the treatment of endometriosis or fibroid tumors of the uterus were effectively eliminated in the treated females by administration of 14α,15α-methylene-1,3,5(10),8-tetraene-

3,17α-diol.
IT **9034-40-6D**, Gonadotropin-releasing hormone, analogs
RL: **ADV (Adverse effect, including toxicity)**; BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified estradiol or modified estriol for treating side effects during and/or after GnRHa therapy)
RN 9034-40-6 CAPLUS
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **979-32-8**, Estra 1,3,5(10)-triene-3,17β-diol-17-valerate
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified estradiol or modified estriol for treating side effects during and/or after GnRHa therapy)
RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L169 ANSWER 2 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:353298 CAPLUS
DOCUMENT NUMBER: 136:350812
TITLE: GnRH analogues for treatment of urinary incontinence and other side effects associated with ovariectomy or reproductive senescence in humans and dogs
INVENTOR(S): Arnold, Susi; Reichler, Iris; Hubler, Madeleine
PATENT ASSIGNEE(S): University of Zurich, Switz.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036144	A1	20020510	WO 2001-CH636	20011026

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,

Hospital Medical School, London, UK.
SOURCE: British journal of obstetrics and gynaecology, (1993 Apr) Vol. 100, No. 4, pp. 360-4.
Journal code: 7503752. ISSN: 0306-5456.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930702
Last Updated on STN: 19930702
Entered Medline: 19930623

ABSTRACT:
OBJECTIVE: To assess whether GnRH analogues are effective in relieving pelvic pain and congestion and whether menopausal symptoms caused by GnRH analogues can be minimised by supplementation with low dose continuous combined hormone replacement therapy (HRT). DESIGN: Open prospective study. SETTING: Tertiary referral clinic at a teaching hospital. PATIENTS: Twenty-one women with chronic pelvic pain. INTERVENTION: Four months' therapy with goserelin 3.6 mg/month combined with continuous oestradiol valerate 1 mg daily and medroxyprogesterone acetate 5 mg daily. MAIN OUTCOME MEASURES: Visual analogue scale for pain, menopausal symptoms, bleeding patterns, uterine area, endometrial status, oestradiol concentrations and venogram scores. RESULTS: Amenorrhoea was maintained in all but two women. Endometrial atrophy was maintained despite HRT supplementation. Two women had moderate menopausal symptoms but none had severe symptoms. Significant reduction of uterine cross sectional area was maintained throughout the study. There was no significant relief of pain. CONCLUSIONS: HRT supplementation of GnRH analogues abolishes menopausal symptoms and thus may improve patient acceptability. Potentially beneficial effects such as endometrial atrophy, reduction of uterine volume and amenorrhoea were not negated by HRT. This combination is not effective in the treatment of chronic pelvic pain and congestion.

CONTROLLED TERM: Check Tags: Female
Adult
Chronic Disease
***Estradiol: AA, analogs & derivatives**
Estradiol: TU, therapeutic use
*Estrogen Replacement Therapy
***Goserelin: AE, adverse effects**
Goserelin: TU, therapeutic use
Humans
Hysterectomy
*Medroxyprogesterone 17-Acetate: TU, therapeutic use
Menopause: DE, drug effects
Pain Measurement
Patient Satisfaction
*Pelvic Inflammatory Disease: DT, drug therapy
Prospective Studies
Time Factors
CAS REGISTRY NO.: 50-28-2 (Estradiol); 65807-02-5 (Goserelin); 71-58-9 (Medroxyprogesterone 17-Acetate); **979-32-8 (estradiol valerate)**

L169 ANSWER 13 OF 41 MEDLINE on STN
ACCESSION NUMBER: 93101379 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8416441
TITLE: The prevention of bone loss in young women treated with GnRH analogues with "add-back" estrogen therapy.
AUTHOR: Leather A T; Studd J W; Watson N R; Holland E F
CORPORATE SOURCE: Premenstrual Syndrome Clinic, Dulwich Hospital, London,

United Kingdom.
SOURCE: Obstetrics and gynecology, (1993 Jan) Vol. 81, No. 1, pp. 104-7.
Journal code: 0401101. ISSN: 0029-7844.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199301
ENTRY DATE: Entered STN: 19930205
Last Updated on STN: 19930205
Entered Medline: 19930121

ABSTRACT:
OBJECTIVE: To determine whether the addition of a low dose of oral estrogen replacement therapy (ERT) taken daily can prevent the bone loss associated with continuous GnRH analogue use. METHODS: In a double-blind, placebo-controlled study, 60 women aged 21-45 years were randomized to one of three treatment groups: placebo implant every 4 weeks plus placebo ERT tablets daily, Zoladex (goserelin 3.6 mg) implant every 4 weeks plus placebo ERT tablets daily, or Zoladex (3.6 mg) implant every 4 weeks plus estradiol valerate, 2 mg/day, with norethisterone 5 mg from days 22-28. A dual x-ray bone density scan was performed before treatment and again after six treatment cycles. The percentage bone change with respect to the initial bone density was calculated. RESULTS: There was a significant loss of bone density at both the lumbar spine and proximal femur in the group receiving Zoladex plus placebo after 6 months compared with both pre-treatment values and with the group receiving placebo plus placebo. The addition of estrogen "add-back" therapy to GnRH analogue treatment (Zoladex plus ERT) resulted in no significant change in bone density compared with either pre-treatment values or the group receiving placebo plus placebo. The study had a dropout rate of 32%. CONCLUSION: The addition of "add-back" estrogen therapy to continuous GnRH analogue use can prevent bone loss.

CONTROLLED TERM: Check Tags: Female
Administration, Oral
Adult
Bone Density
Double-Blind Method
Drug Implants
Estradiol: AD, administration & dosage
Estradiol: AA, analogs & derivatives
*Estrogens: AD, administration & dosage
Goserelin: AD, administration & dosage
***Goserelin: AE, adverse effects**
Humans
Middle Aged
Norethindrone: AD, administration & dosage
Osteoporosis: CI, chemically induced
Osteoporosis: DI, diagnosis
*Osteoporosis: PC, prevention & control
Premenstrual Syndrome: DT, drug therapy
Research Support, Non-U.S. Gov't
CAS REGISTRY NO.: 50-28-2 (Estradiol); 65807-02-5 (Goserelin); 68-22-4 (Norethindrone); **979-32-8 (estradiol valerate)**
CHEMICAL NAME: 0 (Drug Implants); 0 (Estrogens)

L169 ANSWER 14 OF 41 MEDLINE on STN
ACCESSION NUMBER: 94121451 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8291869

TITLE: Polyestradiol phosphate (160 mg/month) or LHRH analog (buserelin depot) in the treatment of locally advanced or metastasized prostatic cancer. The Finnprostate Group.
AUTHOR: Aro J; Ruutu M; Juusela H; Hansson E; Permi J
CORPORATE SOURCE: Malmi Hospital, Helsinki, Finland.
SOURCE: Annales chirurgiae et gynaecologiae. Supplementum, (1993) Vol. 206, pp. 5-8.
Journal code: 7702959. ISSN: 0355-9874.
PUB. COUNTRY: Finland
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940312
Last Updated on STN: 19970203
Entered Medline: 19940224

ABSTRACT:
The clinical efficacy, cardiovascular complications and mortality of polyestradiol phosphate (PEP) 160 mg/month i.m. were compared with the luteinizing hormone releasing hormone (LHRH) analog, buserelin, in a prospective, randomised multicentre study including 147 patients with prostatic cancer. The cumulative non-progression rate at three years was 0.53 in the PEP group and 0.70 in the LHRH group. The mortality from cardiovascular diseases was the same in the two treatment groups. The parenterally given PEP was not associated with an increased risk of cardiovascular complications. The dosage of PEP 160 mg monthly seems, however, to be insufficient in the treatment of prostatic cancer.

CONTROLLED TERM: Check Tags: Male
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: EP, epidemiology
Aged
Buserelin: AD, administration & dosage
Buserelin: AE, adverse effects
*Buserelin: TU, therapeutic use
*Cardiovascular Diseases: CI, chemically induced
Cardiovascular Diseases: EP, epidemiology
Comparative Study
Estradiol: AD, administration & dosage
Estradiol: AE, adverse effects
***Estradiol: AA, analogs & derivatives**
Estradiol: TU, therapeutic use
Estradiol Congeners: AD, administration & dosage
Estradiol Congeners: AE, adverse effects
Estradiol Congeners: TU, therapeutic use
Finland: EP, epidemiology
Humans
Prospective Studies
*Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: EP, epidemiology
Research Support, Non-U.S. Gov't
CAS REGISTRY NO.: 28014-46-2 (polyestradiol phosphate); 50-28-2 (Estradiol); 57982-77-1 (Buserelin)
CHEMICAL NAME: 0 (Estradiol Congeners)

L169 ANSWER 15 OF 41 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 3
ACCESSION NUMBER: 1992-49273 DRUGU T S E

TITLE: A Case of Hidradenitis Suppurativa Treated with **Gonadotropin-Releasing Hormone** Agonist and by Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy.
AUTHOR: Bogers J W; Minderhoud Bassie W; Huikeshoven F J M
LOCATION: Rotterdam, Netherlands
SOURCE: Am.J.Obstet.Gynecol. (167, No. 2, 517-18, 1992) 2 Ref.
CODEN: AJOGAH ISSN: 0002-9378
AVAIL. OF DOC.: Department of Obstetrics and Gynecology, AZR-Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. (F.J.M.H.).
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

A case of hidrandenitis suppurativa (HS) treated successfully with buserelin acetate (BU) and by total abdominal hysterectomy and bilateral salpingo-oophorectomy is reported. Prior unsuccessful treatment included antibacterial drugs, isotretinoin, surgery (full-thickenss skin excision and skinning vulvectomy), oral contraceptives, cyproterone acetate, tamoxifen acetate, p.o. progestogens and medroxyprogesterone acetate depot. BU induced disease regression, with mild vasomotor and other signs of estrogen deprivation. Addition of estradiol valerate did not alter disease remission. Surgical treatment was then carried out followed by estradiol valerate therapy. 6 Mth afterwards the pt was without complaint.

SECTION HEADING: T Therapeutics
S Adverse Effects
E Endocrinology

CLASSIF. CODE: 15 Drugs in Fertility
35 Adverse Reactions
49 Peptide Hormones

CONTROLLED TERM:
[01] BUSERELIN *TR; BUSERELIN ***AE**; HIDRADENITIS *TR; SUPPURATIVE *TR; FLUSHING ***AE**; **ESTRADIOL-VALERATE** *RC; HYSTERECTOMY *FT; SALPINGO-OVARIECTOMY *FT; CASE-HISTORY *FT; IN-VIVO *FT; LULIBERIN-AGONIST *FT; SURGERY *FT; CASES *FT; **RELEASING-FACTOR** *FT; **RELEASING-FACTORS** *FT; LULIBERIN-AGONISTS *FT; BUSERELIN *RN; TR *FT; **AE** *FT
CAS REGISTRY NO.: 57982-77-1
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L169 ANSWER 16 OF 41 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-13640 DRUGU T E S
TITLE: High bone density in hyperandrogenic women: effect of **gonadotropin-releasing hormone** agonist alone or in conjunction with estrogen-progestin replacement.
AUTHOR: Simberg N; Tiitinen A; Silfast A; Viinikka L; Ylikorkala O
LOCATION: Helsinki; Espoo, Fin.
SOURCE: J.Clin.Endocrinol.Metab. (81, No. 2, 646-51, 1996) 4 Fig. 2 Tab. 43 Ref.
CODEN: JCEMAZ ISSN: 0021-972X
AVAIL. OF DOC.: Department of Obstetrics and Gynecology, Helsinki University

Central Hospital, FIN-00290 Helsinki, Finland.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

In a randomized, follow-up study of 20 hirsute women with ovarian hyperandrogenism, showing greater bone mineral density (BMD) than 19 age-matched normal controls, long-term goserelin (Zoladex depot, Zeneca) treatment resulted in a decrease of BMD which was regained after cessation of treatment, or was attenuated in those randomized to receive added estradiol valerate/medroxyprogesterone acetate (HRT, Divina, Orion). Urinary collagen pyridinoline (PY), deoxy-PY cross-links and hydroxyproline (HP) output (markers of bone resorption) increased after short-term GnRF treatment, although BMD and serum levels of collagen type I telopeptide and bone-specific alkaline phosphatase (AP) were not changed. Early changes in serum telopeptide and urinary PY and deoxy-PY were correlated with later decreases in femoral neck BMD.

SECTION HEADING: T Therapeutics
E Endocrinology
S Adverse Effects

CLASSIF. CODE: 24 Bones and Joints
35 Adverse Reactions
47 Sex Hormones
49 Peptide Hormones
64 Clinical Trials

CONTROLLED TERM:
HYPERANDROGENISM *TR; OVARY-DISEASE *TR; HIRSUTISM *TR; CASES *FT; HUMAN *FT; IN-VIVO *FT; RANDOM *FT; BONE *FT; CLIN.TRIAL *FT
[01] GOSERELIN *TR; ZOLADEX *TR; GOSERELIN ***AE**; ZOLADEX ***AE**; ZENECA *FT; OSTEOPATHY ***AE**;
GOSERELIN *RN; DEPOT *FT; LULIBERIN-AGONIST *FT; PHARM.PREP. *FT; **RELEASING-FACTOR** *FT; **RELEASING-FACTORS** *FT; LULIBERIN-AGONISTS *FT; TR *FT; **AE** *FT
CAS REGISTRY NO.: 65807-02-5
[02] **ESTRADIOL-VALERATE** *TR; DIVINA *TR; ORION *FT; OSTEOPATHY *TR; ESTRADIOV *RN; ESTROGEN *FT; COMB.PREP. *FT; ESTROGENS *FT; TR *FT
CAS REGISTRY NO.: **979-32-8**
[03] MEDROXYPROGESTERONE-ACETATE *TR; DIVINA *TR; ORION *FT; OSTEOPATHY *TR; MEDOXPRAC *RN; PROGESTOGEN *FT; COMB.PREP. *FT; PROGESTOGENS *FT; TR *FT
CAS REGISTRY NO.: 71-58-9
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L169 ANSWER 17 OF 41 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1995-44271 DRUGU T E S
TITLE: Steroidal and nonsteroidal "add-back" therapy: extending safety and efficacy of **gonadotropin-releasing hormone** agonists in the gynecologic patient.
AUTHOR: Surrey E S
CORPORATE SOURCE: Univ.California
LOCATION: Beverly Hills; Los Angeles, Cal., USA
SOURCE: Fertil.Steril. (64, No. 4, 673-85, 1995) 3 Fig. 6 Tab. 87

Ref.

CODEN: FESTAS ISSN: 0015-0282
AVAIL. OF DOC.: Center for Reproductive Medicine and Surgery, 9675 Brighton Way, Suite 420, Beverly Hills, California 90210, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The use of steroidal and non-steroidal add-back therapy to reduce the hypoestrogenic side-effects of long-term GnRF agonists in gynecologic patients is reviewed. The **cardiovascular** risks, vasomotor symptoms and effects on bone mineral density (BMD) of long-term GnRF therapy are described. The rationale for add-back therapy with estrogens, progestogens and other agents is discussed with reference to clinical studies of conjugated equine estrogens (CEE), estropipate, estradiol (E2), E2 valerate, medroxyprogesterone acetate (MPA), norethindrone, norgestrel, norethisterone, sodium etidronate and calcium carbonate, salmon calcitonin and tamoxifen in patients taking long-term goserelin acetate, Decapeptyl, nafarelin acetate, buserelin acetate, histrelin acetate and leuprorelin.

SECTION HEADING: T Therapeutics
E Endocrinology
S Adverse Effects

CLASSIF. CODE: 15 Drugs in Fertility
35 Adverse Reactions
47 Sex Hormones
49 Peptide Hormones
64 Clinical Trials
69 Reviews

CONTROLLED TERM:
GYNECOLOGY *TR; UTERUS-DISEASE *TR; VASCULAR-DISEASE *
AE; OSTEOPOROSIS ***AE**; OSTEOPOROSIS *TR;
VASCULAR-DISEASE *TR; OSTEOPATHY ***AE**; OSTEOPATHY
*TR; CASES *FT; REVIEW *FT; IN-VIVO *FT; ESTROGEN *FT;
PROGESTOGEN *FT; LULIBERIN-AGONIST *FT; **RELEASING-FACTOR**
*FT
[01] MAIN-TOPIC *FT; ESTROGENS *FT; PROGESTOGENS *FT;
LULIBERIN-AGONISTS *FT; COMB. *FT; CLIN.TRIAL *FT;
RELEASING-FACTORS *FT; TR *FT; **AE** *FT
[02] ENDOMETRIOSIS *TR; LEIOMYOMA *TR; HIRSUTISM *TR;
PREMENSTRUAL-TENSION *TR; GYNECOLOGY *TR; NEOPLASM *TR;
MENTAL-DISORDER *TR; MENSTRUATION *TR; LEUPRORELIN *
AE; LEUPRORELIN *TR; NAFARELIN ***AE**;
TRIPTORELIN ***AE**; DECAPEPTYL ***AE**;
DECAPEPTYL ***AE**; BUSERELIN ***AE**; GOSERELIN
***AE**; MEDROXYPROGESTERONE-ACETATE *TR;
ESTROGEN-CONJUGATED *TR; ESTROPIPATE *TR; NORETHISTERONE *TR;
ESTRADIOL *TR; **ESTRADIOL-VALERATE** *TR; NORGESTREL
*TR; NORETHISTERONE *TR; GOSERELIN *TR; TRIPTORELIN *TR;
DECAPEPTYL *TR; DECAPEPTYL *TR; BUSERELIN *TR; HISTRELIN *TR;
NORETHISTERONE ***AE**; MEDROXYPROGESTERONE-ACETATE *
AE; ETIDRONATE *TR; CALCIUM-CARBONATE *TR; CALCITONIN
*TR; TAMOXIFEN *TR; TR *FT; **AE** *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L169 ANSWER 18 OF 41 DRUGU

ACCESSION NUMBER: 1994-32331 DRUGU T E S
TITLE: Menstrual asthma: use of a **gonadotropin-releasing hormone** analog for the treatment of cyclic aggravation of bronchial asthma.
AUTHOR: Blumenfeld Z; Bentur L; Yoffe N; Alroy G; Rubin A H E
CORPORATE SOURCE: Inst.Technol.Haifa
LOCATION: Haifa, Israel
SOURCE: Fertil.Steril. (62, No. 1, 197-200, 1994) 1 Tab. 6 Ref.
CODEN: FESTAS ISSN: 0015-0282
AVAIL. OF DOC.: No Reprint Address
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

I.m. depot triptorelin (Decapeptyl CR, Ferring) treatment was successfully used to treat severe cyclic asthma during ovulation and menstruation. The side-effects were amenorrhea and hot flushes. The patient also received p.o. prednisone, theophylline, inhaled beclometasone dipropionate (Becotide, Glaxo) and inhaled salbutamol (Ventolin, Glaxo), and cimetidine (Cimetag, Teva) for a peptic ulcer. Sequential hormone replacement with estradiol valerate and norgestrel (Progyluton, Schering-Berlin) aggravated respiratory symptoms, but low-dose estrogen (Premarin, Dexon) plus medroxyprogesterone acetate (Aragest, Dexon), to prevent osteoporosis, was better tolerated.

SECTION HEADING: T Therapeutics
E Endocrinology
S Adverse Effects

CLASSIF. CODE: 15 Drugs in Fertility
33 Respiratory
35 Adverse Reactions
47 Sex Hormones
49 Peptide Hormones

CONTROLLED TERM:
PREDNISONE *RC; THEOPHYLLINE *RC; BECLOMETASONE-DIPROPIONATE *RC; BECOTIDE *RC; SALBUTAMOL *RC; VENTOLIN *RC; CIMETIDINE *RC; CASE-HISTORY *FT; IN-VIVO *FT; CASES *FT
[01] TRIPTORELIN *TR; DECAPEPTYL *TR; TRIPTORELIN ***AE**; DECAPEPTYL ***AE**; FERRING *FT; ASTHMA *TR; FLUSHING * **AE**; AMENORRHEA ***AE**; PNEUMOPATHY *TR; GYNECOLOGY ***AE**; MENSTRUATION ***AE**; WY-42462 *RN; LULIBERIN-AGONIST *FT; I.M. *FT; DEPOT *FT; MENSTRUATION *FT; OVULATION *FT; **RELEASING-FACTOR** *FT; INJECTION *FT; PHARM.PREP. *FT; OVARY *FT; **RELEASING-FACTORS** *FT; LULIBERIN-AGONISTS *FT; TR *FT; **AE** *FT
CAS REGISTRY NO.: 57773-63-4
[02] **ESTRADIOL-VALERATE** *TR; ESTRADIOL-VALERATE * **AE**; PROGYLUTON *TR; PROGYLUTON ***AE**; SCHERING-BERLIN *FT; ASTHMA ***AE**; PNEUMOPATHY * **AE**; ESTRADIOV *RN; COMB. *FT; ESTROGEN *FT; ESTROGENS *FT; TR *FT; **AE** *FT
CAS REGISTRY NO.: **979-32-8**
[03] NORGESTREL *TR; NORGESTREL ***AE**; PROGYLUTON *TR; PROGYLUTON ***AE**; SCHERING-BERLIN *FT; ASTHMA * **AE**; PNEUMOPATHY ***AE**; NORGESTRE *RN; COMB. *FT; PROGESTOGEN *FT; PROGESTOGENS *FT; TR *FT; **AE** *FT

CAS REGISTRY NO.: 6533-00-2
[04] MEDROXYPROGESTERONE-ACETATE *TR; ARAGEST *TR; OSTEOPOROSIS *TR; OSTEOPATHY *TR; MEDOXPRAC *RN; DEXON *FT; PROGESTOGEN *FT; PROPHYLAXIS *FT; PROGESTOGENS *FT; TR *FT
CAS REGISTRY NO.: 71-58-9
[05] ESTROGEN-CONJUGATED *TR; PREMARIN *TR; OSTEOPOROSIS *TR; OSTEOPATHY *TR; ESTROCONJ *RN; DEXON *FT; PROPHYLAXIS *FT; ESTROGEN *FT; ESTROGENS *FT; TR *FT
CAS REGISTRY NO.: 12126-59-9
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L169 ANSWER 19 OF 41 DRUGU COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-42641 DRUGU T E S
TITLE: Estrogen replacement does not potentiate **gonadotropin -releasing hormone** agonist-induced androgen suppression in treatment of hirsutism.
AUTHOR: Tiitinen A; Simberg N; Stenman U H; Ylikorkala O
CORPORATE SOURCE: Univ.Helsinki
LOCATION: Helsinki, Finland
SOURCE: J.Clin.Endocrinol.Metab. (79, No. 2, 447-51, 19 2 Fig. 2 Tab. 29 Ref.
CODEN: JCEMAZ ISSN: 0021-972X
AVAIL. OF DOC.: Department of Obstetrics and Gynecology, Helsinki University Central Hospital, FIN-00290 Helsinki, Finland.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

Estrogen replacement with estradiol valerate plus medroxyprogesterone acetate (EV + MA: Divina; Orion) did not potentiate the therapeutic effect of androgen suppression with s.c. implanted goserelin (GS: Zoladex; Zeneca) among 20 hirsute women (18 with polycystic ovary: PCO) during a randomized parallel-group trial. Estrogen replacement restored serum estradiol (E2) levels and increased sex hormone-binding globulin (SHBG) but did not decrease free testosterone (TS) levels. Estrogen replacement abolished or alleviated the hypoestrogenic vasomotor symptoms caused by GS, but itself caused bleeding, headache and premenstrual tension. Thus, estrogenic alleviation of ovarian hyperandrogenism may involve suppressing gonadotropins rather than increasing SHBG.

SECTION HEADING: T Therapeutics
E Endocrinology
S Adverse Effects

CLASSIF. CODE: **35 Adverse Reactions**
47 Sex Hormones
49 Peptide Hormones
64 Clinical Trials

CONTROLLED TERM:
HIRSUTISM *TR; HYPERANDROGENISM *TR; POLYCYSTIC-OVARY *TR; OVARY-DISEASE *TR; CASES *FT; IN-VIVO *FT; CONCOMITANT-DISEASE *FT; RANDOM *FT; CLIN.TRIAL *FT; LONG-TERM-THERAPY *FT
[01] GOSERELIN *TR; ZOLADEX *TR; GOSERELIN ***AE**; ZOLADEX ***AE**; HYPOESTROGENIC ***AE**; VASOMOTOR ***AE**; FLUSHING ***AE**; SWEATING ***AE**; LIBIDO ***AE**; DEPRESSION ***AE**; SWEAT *

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2427731	AA	20020510	CA 2001-2427731	20011026
AU 2001095359	A5	20020515	AU 2001-95359	20011026
EP 1330257	A1	20030730	EP 2001-975948	20011026
EP 1330257	B1	20050831		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

BR 2001015067	A	20040406	BR 2001-15067	20011026
JP 2004512369	T2	20040422	JP 2002-538955	20011026
AT 303156	E	20050915	AT 2001-975948	20011026
US 2004023878	A1	20040205	US 2003-415519	20030430
PRIORITY APPLN. INFO.:			EP 2000-811011 A	20001030
			WO 2001-CH636 W	20011026

ED Entered STN: 12 May 2002

AB The use of at least one GnRH analog for the preparation of a medicament for the prevention and/or treatment of side effects of ovariectomy or symptoms associated with reproductive senescence in female mammals, in particular urinary incontinence, hot flushes, and skin/hair changes are disclosed. The GnRH analog is selected from the group consisting of deslorelin acetate, goserelin acetate, nafarelin acetate, buserelin acetate, triptorelin acetate, gonadorelin acetate, leuprolid acetate, danazolum, Cetrorelix or mixts. thereof. The medicament can further comprise another active substance selected from the group consisting of an estrogenic agent, a partial estrogenic agent, a progestational agent, or mixts. thereof. The addnl. active ingredient can also be an α-adrenergic agonist, a β-adrenergic receptor blocking agent, a cholinergic receptor blocking compound, a cholinergic receptor stimulating drug, a smooth muscle relaxant, a nitric oxide synthase substrate, a nitric oxide donor, or mixts. thereof.

IT **9034-40-6D**, GnRH, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GnRH analogs for treatment of urinary incontinence and other side effects associated with ovariectomy or reproductive senescence in humans and dogs)

RN 9034-40-6 CAPLUS

CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

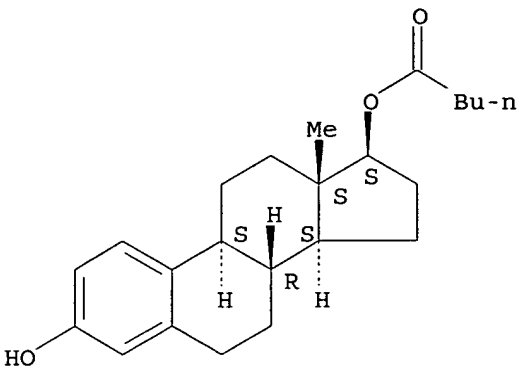
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **979-32-8**, Estradiol valerate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GnRH analogs in combination with other active ingredients for treatment of urinary incontinence and other side effects associated with ovariectomy or reproductive senescence in humans and dogs)

RN 979-32-8 CAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



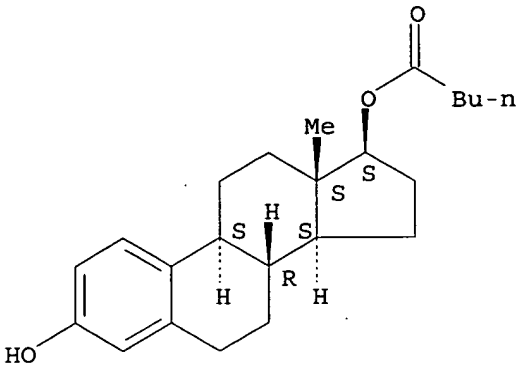
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L169 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:99929 CAPLUS
DOCUMENT NUMBER: 144:177480
TITLE: Pharmaceutical-encapsulated nanoparticles for transmucosal absorption
INVENTOR(S): Mizushima, Hiroshi; Ueno, Yukio; Udagawa, Masae; Kameyama, Mieko; Suzuki, Yoshiki; Sekine, Junzo
PATENT ASSIGNEE(S): Ltt Biopharma Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 19 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2006028031	A2	20060202	JP 2004-205259	20040712
PRIORITY APPLN. INFO.:			JP 2004-205259	20040712

ED Entered STN: 03 Feb 2006
AB Title nanoparticles contain divalent metal salts, hydrophobic substances, and/or sugars, and pharmaceuticals encapsulated in cores having CO2H on the surface. Thus, rhodamine-encapsulated, carboxylated polystyrene nanoparticles were treated with CaCl2 to give secondary nanoparticles with particle size 50 nm, which were almost completely absorbed from jejunum in mice.
IT **979-32-8**, Estradiol valerate **9034-40-6**, Luteinizing hormone-releasing hormone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transmucosal carboxylated nanoparticles with high drug bioavailability)
RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9034-40-6 CAPLUS
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L169 ANSWER 4 OF 41 USPATFULL on STN
ACCESSION NUMBER: 2004:31736 USPATFULL
TITLE: Gnrh analogues for treatment of urinary incontinence
INVENTOR(S): Arnold, Susi, UNITED STATES
Reichler, Iris, Z?uuml;rich, SWITZERLAND
Hubler, Madeleine, Wernetshausen, SWITZERLAND

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004023878	A1	20040205	
APPLICATION INFO.:	US 2003-415519	A1	20030430	(10)
	WO 2001-CH636		20011026	

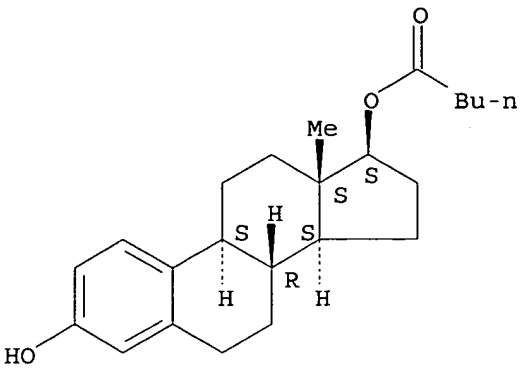
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROTHWELL, FIGG, ERNST & MANBECK, P.C., 1425 K STREET, N.W., SUITE 800, WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 826
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use of at least one GnRH analogue for the preparation of a medicament for the prevention and/or treatment of side effects of ovarectomy or symptoms associated with reproductive senescence in female mammals, in particular urinary incontinence, hot flushes, and skin/hair changes are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **9034-40-6D**, GnRH, analogs
(GnRH analogs for treatment of urinary incontinence and other side effects associated with ovariectomy or reproductive senescence in humans and dogs)
RN 9034-40-6 USPATFULL
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE
IT **979-32-8**, Estradiol valerate
(GnRH analogs in combination with other active ingredients for treatment of urinary incontinence and other side effects associated with ovariectomy or reproductive senescence in humans and dogs)

RN 979-32-8 USPATFULL
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L169 ANSWER 5 OF 41 USPATFULL on STN

ACCESSION NUMBER:	2003:129817 USPATFULL
TITLE:	Methods and compositions for disrupting the epithelial barrier function
INVENTOR(S):	Elias, Peter M., Muir Beach, CA, United States Feingold, Kenneth R., Saan Rafael, CA, United States Holleran, Walter M., San Francisco, CA, United States
PATENT ASSIGNEE(S):	The Regents of the University of California, Oakland, CA, United States (U.S. corporation) Cellegy Pharmaceuticals, Inc., Foster City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6562606	B1	20030513
APPLICATION INFO.:	US 2000-608568		20000630 (9)

RELATED APPLN. INFO.:	Continuation of Ser. No. US 1998-58401, filed on 9 Apr 1998, now patented, Pat. No. US 6190894 Continuation of Ser. No. US 1996-733712, filed on 23 Oct 1996, now abandoned Continuation-in-part of Ser. No. US 1994-260559, filed on 16 Jun 1994, now abandoned Continuation-in-part of Ser. No. US 1993-33811, filed on 19 Mar 1993, now abandoned
DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Lankford, Jr., Leon B.
LEGAL REPRESENTATIVE:	Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS:	23
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT:	1114

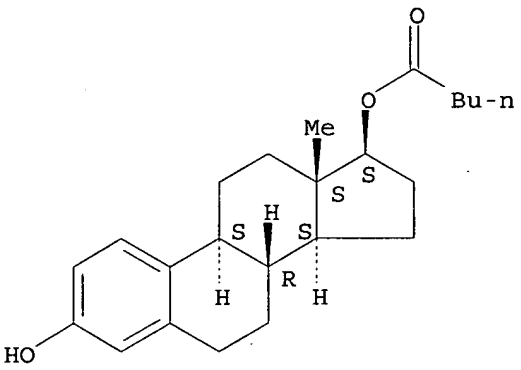
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for disrupting epithelial barrier function in a host in need of the topical administration of a physiologically active substance which comprises applying to the epithelium of the host, barrier-disrupting amount of at least one agent selected from the group consisting of an inhibitor of ceramide synthesis, inhibitor of acylceramide synthesis, inhibitor of glucosylceramide synthesis, and inhibitor of sphingomyelin

synthesis, an inhibitor of fatty acid synthesis, an inhibitor of cholesterol synthesis, a degradation enzyme of ceramides, acylceramide, glucosylceramides, sphingomyelin, an inhibitor of phospholipid, glycosphingolipid, including glucosylceramide, acylceramide or sphingomyelin degradation, and both inhibitors and stimulators of metabolic enzymes of free fatty acids, ceramide, and cholesterol, as well as a topical composition useful therefor are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **979-32-8**, Estradiol valerate **9034-40-6**, Lhrh
(permeation enhancement of topical pharmaceuticals by inducing phase separation of epithelial lipid bilayers)
RN 979-32-8 USPATFULL
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9034-40-6 USPATFULL
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L169 ANSWER 6 OF 41 USPATFULL on STN
ACCESSION NUMBER: 2001:25659 USPATFULL
TITLE: Method and compositions for disrupting the epithelial barrier function
INVENTOR(S): Thornfeldt, Carl R., Nampa, ID, United States
Elias, Peter M., Muir Beach, CA, United States
Feingold, Kenneth R., Saan Rafael, CA, United States
Holleran, Walter M., San Francisco, CA, United States
PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)
Cellegy Pharmaceuticals, Inc., Foster City, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6190894	B1	20010220
APPLICATION INFO.:	US 1998-58401		19980409 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-733712, filed on 23 Oct 1996, now abandoned Continuation-in-part of Ser. No. US 1994-260559, filed on 16 Jun 1994, now abandoned Continuation-in-part of Ser. No. US 1993-33811, filed on 19 Mar 1993, now abandoned

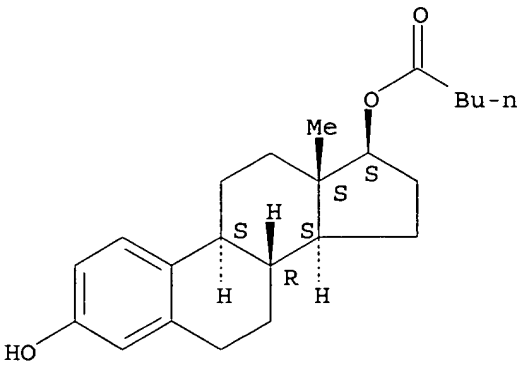
Searched by Barb O'Bryen, STIC 2-2518

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lankford, Jr., Leon B.
LEGAL REPRESENTATIVE: Townsend and Townsend and Crew LLP
NUMBER OF CLAIMS: 82
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1469
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for disrupting epithelial barrier function in a host in need of the topical administration of a physiologically active substance which comprises applying to the epithelium of the host, barrier-disrupting amount of at least one agent selected from the group consisting of an inhibitor of ceramide synthesis, inhibitor of acylceramide synthesis, inhibitor of glucosylceramide synthesis, and inhibitor of sphingomyelin synthesis, an inhibitor of fatty acid synthesis, an inhibitor of cholesterol synthesis, a degradation enzyme of ceramides, acylceramide, glucosylceramides, sphingomyelin, an inhibitor of phospholipid, glycosphingolipid, including glucosylceramide, acylceramide or sphingomyelin degradation, and both inhibitors and stimulators of metabolic enzymes of free fatty acids, ceramide, and cholesterol, as well as a topical composition useful therefore are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **979-32-8**, Estradiol valerate **9034-40-6**, Lhrh
(permeation enhancement of topical pharmaceuticals by inducing phase separation of epithelial lipid bilayers)
RN 979-32-8 USPATFULL
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9034-40-6 USPATFULL
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L169 ANSWER 7 OF 41 USPATFULL on STN
ACCESSION NUMBER: 94:73073 USPATFULL
TITLE: Method and formulations for use in treating benign gynecological disorders
INVENTOR(S): Pike, Malcolm C., Long Beach, CA, United States
Spicer, Darcy V., Pasadena, CA, United States
PATENT ASSIGNEE(S): University of Southern California, Los Angeles, CA,

United States (U.S. corporation)

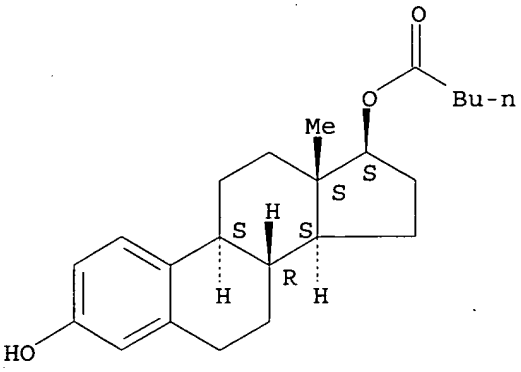
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5340585		19940823
APPLICATION INFO.:	US 1993-62883		19930517 (8)

DISCLAIMER DATE: 20100518
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1992-952513, filed on 3 Dec 1992 which is a continuation-in-part of Ser. No. US 1991-684612, filed on 12 Apr 1991, now patented, Pat. No. US 5211952
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Azpuru, Carlos
LEGAL REPRESENTATIVE: Robbins, Berliner & Carson
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 901
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods which are effective to treat benign gynecological disorders for extended periods of time in women in who the risk of endometrial stimulation is minimized or absent are described, wherein an effective amount of a gonadotropin hormone releasing hormone composition and an effective amount of an estrogenic composition are provided over a period of time, optionally with addition of an androgenic composition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **979-32-8**, Estradiol valerate **9034-40-6**, Gonadotropin releasing hormone
(GnRH composition and estrogenic composition combination for treatment of benign gynecol. disorders)
RN 979-32-8 USPATFULL
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 9034-40-6 USPATFULL
CN Luteinizing hormone-releasing factor (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L169 ANSWER 8 OF 41 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 92103021 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1836959
TITLE: The combination of a depot gonadotrophin releasing hormone agonist and cyclical hormone replacement therapy for dysfunctional uterine bleeding.
AUTHOR: Thomas E J; Okuda K J; Thomas N M
CORPORATE SOURCE: Department of Obstetrics and Gynaecology, Newcastle General Hospital, Newcastle-upon-Tyne.
SOURCE: British journal of obstetrics and gynaecology, (1991 Nov) Vol. 98, No. 11, pp. 1155-9.
Journal code: 7503752. ISSN: 0306-5456.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199202
ENTRY DATE: Entered STN: 19920302
Last Updated on STN: 19920302
Entered Medline: 19920212

ABSTRACT:
OBJECTIVE--To observe if a combination of a depot GnRH agonist and cyclical hormone replacement therapy decreases menstrual blood loss. DESIGN--An open, observational study comparing the objective assessment of menstrual blood loss before, during and after 3 months treatment. SUBJECTS--20 women with a subjective complaint of heavy menstrual loss in whom no cause could be discovered. INTERVENTIONS--Each woman received 3 months of depot goserelin (Zoladex) combined with cyclical hormone replacement therapy (Cyclo-Progynova, 1 mg). Menstrual loss and symptoms were assessed before, throughout and after the study. MAIN OUTCOME MEASURES--Changes in objective and subjective assessments of menstrual blood loss and the acceptability of the treatment. RESULTS--The median pretreatment menstrual loss was 68 ml (range 23-397). Only 8 (40%) of the patients had a loss exceeding 80 ml per period. The median blood loss was 30 ml, 16 ml, and 17 ml in the three treatment cycles (P less than 0.001 Wilcoxon rank sum for the third cycle). There was a significant decrease in the median length of menstruation (P less than 0.001) and the number of towels or tampons (P less than 0.01) used per period in the third treatment cycle. There was a significant decrease (P less than 0.005) in the number of women complaining of dysmenorrhoea, premenstrual symptoms, flooding and the passage of clots. Seventeen patients experienced hot flushes. Eighteen of the 20 patients were completely satisfied with the treatment and would have been happy to continue with it for longer than 12 months. CONCLUSIONS--The combination of a depot gonadotrophin releasing hormone agonist and cyclical hormone replacement therapy is a successful and acceptable treatment of dysfunctional uterine bleeding.

CONTROLLED TERM: Check Tags: Female
Adult
Buserelin: AD, administration & dosage
Buserelin: AE, adverse effects
*Buserelin: AA, analogs & derivatives
Buserelin: TU, therapeutic use
Drug Therapy, Combination
Estradiol: AD, administration & dosage
Estradiol: AE, adverse effects
***Estradiol: AA, analogs & derivatives**
Estradiol: TU, therapeutic use
Goserelin

Searched by Barb O'Bryen, STIC 2-2518

Humans
Injections, Subcutaneous
*Menorrhagia: DT, drug therapy
Middle Aged
Prospective Studies
Research Support, Non-U.S. Gov't
Treatment Outcome

CAS REGISTRY NO.: 50-28-2 (Estradiol); 57982-77-1 (Buserelin); 65807-02-5 (Goserelin); **979-32-8 (estradiol valerate)**

L169 ANSWER 9 OF 41 MEDLINE on STN
ACCESSION NUMBER: 2003111427 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12623503
TITLE: Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer -- Scandinavian Prostatic Cancer Group (SPCG) Study Number 5.
AUTHOR: Hedlund Per Olov; Ala-Opas Martti; Brekkan Einar; Damber Jan Erik; Damber Lena; Hagerman Inger; Haukaas Svein; Henriksson Peter; Iversen Peter; Pousette Ake; Rasmussen Finn; Salo Jaakko; Vaage Sigmund; Varenhorst Eberhard
CORPORATE SOURCE: Department of Urology, Karolinska Hospital, Stockholm, Sweden. (Scandinavian Prostatic Cancer Group). krea@beta.telenordia.se
SOURCE: Scandinavian journal of urology and nephrology, (2002) Vol. 36, No. 6, pp. 405-13.
Journal code: 0114501. ISSN: 0036-5599.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030308
Last Updated on STN: 20030517
Entered Medline: 20030516

ABSTRACT:
OBJECTIVE: In the mid-1980s, interest in parenteral estrogen therapy for prostate cancer was renewed when it was found that it influenced liver metabolism only marginally and had very few cardiovascular side-effects. In this study high-dose polyestradiol phosphate (PEP; Estradurin) was compared to combined androgen deprivation (CAD) for the treatment of patients with metastatic prostate cancer. The aim of the study was to compare anticancer efficacy and adverse events, especially cardiovascular side-effects. MATERIAL AND METHODS: A total of 917 patients with T0-4, NX, M1, G1-3 prostate cancer and an Eastern Cooperative Oncology Group performance status of 0-2 were randomized to treatment with either PEP 240 mg i.m. twice a month for 2 months and thereafter once a month or flutamide (Eulexin) 250 mg t.i.d. per os in combination with either triptorelin (Decapeptyl) 3.75 mg per month i.m. or, on an optional basis, bilateral orchidectomy. A total of 556 patients had died at the time of this analysis. RESULTS: There was no difference between the treatment arms in terms of time to biochemical or clinical progression and overall or disease-specific survival. There was no increase in cardiovascular mortality in the PEP arm. The PEP group had a higher prevalence of cardiovascular disease prior to the study and a significantly higher incidence of non-fatal ischemic heart events and heart decompensation during the study. CONCLUSIONS: PEP has an equal anticancer efficacy to CAD and does not increase cardiovascular mortality. Final evaluation of cardiovascular morbidity is awaiting further analysis and follow-up. PEP is considerably cheaper than CAD.

CONTROLLED TERM: Check Tags: Male
Aged
*Androgen Antagonists: AD, administration & dosage
Androgen Antagonists: AE, adverse effects
Antineoplastic Agents, Hormonal: AD, administration & dosage
Antineoplastic Agents, Hormonal: AE, adverse effects
Cardiovascular Diseases: CI, chemically induced
Comparative Study
Disease Progression
Drug Therapy, Combination
*Estradiol: AD, administration & dosage
*Estradiol: AE, adverse effects
***Estradiol: AA, analogs & derivatives**
*Estradiol Congeners: AD, administration & dosage
*Estradiol Congeners: AE, adverse effects
Flutamide: AD, administration & dosage
Flutamide: AE, adverse effects
Humans
Injections, Intravenous
*Orchiectomy
Prostatic Neoplasms: MO, mortality
*Prostatic Neoplasms: TH, therapy
Research Support, Non-U.S. Gov't
Triptorelin: AD, administration & dosage
Triptorelin: AE, adverse effects

CAS REGISTRY NO.: 13311-84-7 (Flutamide); 28014-46-2 (polyestradiol phosphate); 50-28-2 (Estradiol); 57773-63-4 (Triptorelin)

CHEMICAL NAME: 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); 0 (Estradiol Congeners)

L169 ANSWER 10 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2000165076 MEDLINE

DOCUMENT NUMBER: PubMed ID: 10699602

TITLE: Parenteral estrogen versus total androgen ablation in the treatment of advanced prostate carcinoma: effects on overall survival and cardiovascular mortality. The Scandinavian Prostatic Cancer Group (SPCG)-5 Trial Study.

AUTHOR: Hedlund P O; Henriksson P

CORPORATE SOURCE: Department of Urology, Karolinska Hospital, Stockholm, Sweden.

SOURCE: Urology, (2000 Mar) Vol. 55, No. 3, pp. 328-33.
Journal code: 0366151. E-ISSN: 1527-9995.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20010521
Entered Medline: 20000331

ABSTRACT:
OBJECTIVES: To compare the effect on overall survival of total androgen ablation (TAA) with that of parenteral estrogen and to pay special attention to cardiovascular mortality. TAA (orchiectomy or a luteinizing hormone-releasing hormone analogue combined with an antiandrogen) has been proposed as superior to other endocrine treatments for patients with prostate carcinoma. Recently, the use of parenteral estrogen has been suggested to reduce or even negate the

well-known cardiovascular side effects of oral estrogens. METHODS: Nine hundred fifteen patients were randomized to intramuscular injections of 240 mg polyestradiol phosphate (PEP) every second week for the first 8 weeks (5 doses) followed by a maintenance dose of 240 mg every month (n = 458) or to bilateral orchiectomy or triptorelin 3.75 mg every month combined with the antiandrogen flutamide 250 mg three times daily. The choice between orchiectomy and triptorelin was at the discretion of the clinician and patient. Patients were stratified according to performance status, presence of cardiovascular disease, and alkaline phosphatase level. An observer totally unaware of the treatment given classified all deceased patients. RESULTS: At a median follow-up of 18.5 months, no signs of a difference in overall survival were found between TAA and PEP (P <0.001). Of 458 patients, 266 (58.1%) had died in the PEP group compared with 269 (58.9%) of 457 patients in the TAA group. Within the TAA group, no difference in overall survival existed between patients who had undergone orchiectomy or who were given triptorelin. Furthermore, no differences in cardiovascular mortality were found (3.5% in the PEP group and 3.1% in the TAA group). CONCLUSIONS: The current parenteral estrogen regimen seems to be of comparable efficacy and cardiovascular safety as TAA in terms of overall survival. PEP has by far the lowest drug cost and also the lowest cumulative direct costs and thus has the highest cost-effectiveness. We suggest that parenteral estrogen be included as a therapeutic option in the endocrine management of prostate carcinoma.

CONTROLLED TERM: Check Tags: Male
Aged
Alkaline Phosphatase: BL, blood
*Androgen Antagonists: AD, administration & dosage
Androgen Antagonists: AE, adverse effects
*Antineoplastic Agents, Hormonal: AD, administration & dosage
Antineoplastic Agents, Hormonal: AE, adverse effects
Cardiovascular Diseases: MO, mortality
Comparative Study
Estradiol: AD, administration & dosage
Estradiol: AE, adverse effects
***Estradiol: AA, analogs & derivatives**
*Estradiol Congeners: AD, administration & dosage
Estradiol Congeners: AE, adverse effects
*Flutamide: AD, administration & dosage
Flutamide: AE, adverse effects
Humans
Injections, Intramuscular
*Orchiectomy
Prostatic Neoplasms: MO, mortality
*Prostatic Neoplasms: TH, therapy
Research Support, Non-U.S. Gov't
Survival Rate
*Triptorelin: AD, administration & dosage
Triptorelin: AE, adverse effects

CAS REGISTRY NO.: 13311-84-7 (Flutamide); 28014-46-2 (polyestradiol phosphate); 50-28-2 (Estradiol); 57773-63-4 (Triptorelin)

CHEMICAL NAME: 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); 0 (Estradiol Congeners); EC 3.1.3.1 (Alkaline Phosphatase)

L169 ANSWER 11 OF 41 MEDLINE on STN
ACCESSION NUMBER: 95025705 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7939468
TITLE: Comparison of a long-acting LHRH agonist and polyoestradiol phosphate in the treatment of advanced prostatic carcinoma. An open prospective, randomized multicentre study.

AUTHOR: Lukkarinen O; Kontturi M
CORPORATE SOURCE: Urological Unit, University of Oulu, Finland.
SOURCE: Scandinavian journal of urology and nephrology, (1994 Jun) Vol. 28, No. 2, pp. 171-8.
Journal code: 0114501. ISSN: 0036-5599.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19941222
Entered Medline: 19941028

ABSTRACT:
In a prospective, randomized open study, a long-acting LHRH agonist (Zoladex) was compared with polyoestradiol phosphate (Estradurin), both widely used in Finland for palliative treatment of prostatic carcinoma, as regards efficacy and side effects. Of the 236 enrolled patients, 129 were randomized to receive LHRH agonist and 107 to oestrogen treatment. The median follow-up was 25 months. Reduction of prostatic volume was quicker and more effective in the LHRH than in the oestrogen group, and serum testosterone concentrations fell to castration level after 1 month and 1 year, respectively. In locally advanced (M0) and histologically well or moderately differentiated tumours, LHRH agonist therapy was considerably more effective than oestrogen as regards time to progression of the carcinoma, but in metastatic (M1) and histologically poorly differentiated tumours both methods gave similar results. Cardiovascular complications showed equal incidence in both groups. LHRH agonist therapy thus seemed to be more effective than polyoestradiol phosphate against locally advanced prostatic cancer in the doses used.

CONTROLLED TERM: Check Tags: Male
Aged
Aged, 80 and over
Antineoplastic Agents: AE, adverse effects
*Antineoplastic Agents: TU, therapeutic use
Comparative Study
Estradiol: AE, adverse effects
***Estradiol: AA, analogs & derivatives**
Estradiol: TU, therapeutic use
Goserelin: AE, adverse effects
*Goserelin: TU, therapeutic use
Humans
Middle Aged
Prospective Studies
*Prostatic Neoplasms: DT, drug therapy
Testosterone: BL, blood
CAS REGISTRY NO.: 28014-46-2 (polyestradiol phosphate); 50-28-2 (Estradiol); 58-22-0 (Testosterone); 65807-02-5 (Goserelin)
CHEMICAL NAME: 0 (Antineoplastic Agents)

L169 ANSWER 12 OF 41 MEDLINE on STN
ACCESSION NUMBER: 93264361 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8494837
TITLE: An alternative to hysterectomy? GnRH analogue combined with hormone replacement therapy.
AUTHOR: Gangar K F; Stones R W; Saunders D; Rogers V; Rae T; Cooper S; Beard R W
CORPORATE SOURCE: Department of Obstetrics and Gynaecology, St Mary's

ACCESSION NUMBER: 1982:12222175 BIOTECHNO
TITLE: Effect of cortisol or adrenocorticotrophin on release of luteinizing hormone induced by **luteinizing** hormone **releasing hormone** in the dairy heifer
AUTHOR: Matteri R.L.; Moberg G.P.
CORPORATE SOURCE: Dept. Anim. Sci., Univ. California, Davis, CA 95616, United States.
SOURCE: Journal of Endocrinology, (1982), 92/1 (141-146)
CODEN: JOENAK
DOCUMENT TYPE: Journal; Article
COUNTRY: United Kingdom
LANGUAGE: English
ABSTRACT: During treatment with cortisol or ACTH, dairy heifers were given two doses of LH releasing hormone (LH-RH) spaced 1.5 h apart. Serum concentrations of cortisol and LH were monitored during each treatment. Treatment with both ACTH and cortisol raised plasma cortisol levels above the respective saline controls ($P<0.001$). Neither treatment affected basal LH concentrations. A slight **depression** in LH response was seen in the cortisol-treated animals after the first LH-RH injection, as shown by a statistically significant **depression** at three of the sample times. There was no significant difference between treated and control LH values after the second LH-RH administration. Treatment with ACTh resulted in significantly reduced LH values at all sample times after both injections of LH-RH.
CONTROLLED TERM: *corticotropin; *dexamethasone; ***estradiol valerate**; ***gonadorelin**; *hydrocortisone; *hydrocortisone sodium succinate; *luteinizing hormone; *progesterone; *tetracosactide; drug mixture; luteinizing hormone i 125; animal experiment; cattle; endocrine system
CAS REGISTRY NUMBER: (corticotropin) 11136-52-0, 9002-60-2, 9061-27-2; (dexamethasone) 50-02-2; (**estradiol valerate**) **979-32-8**; (**gonadorelin**) 33515-09-2, **9034-40-6**; (hydrocortisone) 50-23-7; (hydrocortisone sodium succinate) 125-04-2, 2203-97-6; (luteinizing hormone) 39341-83-8, 9002-67-9; (progesterone) 57-83-0; (tetracosactide) 16960-16-0
CHEMICAL NAME: Drug Trade Name: delestrogen; solu cortef; adrenomone
CORPORATE NAME: Drug Manufacturer: sigma, United States; calbiochem, United States; squibb, United States; burns biotec, United States; upjohn, United States

L169 ANSWER 25 OF 41 IPA COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 97:2070 IPA
DOCUMENT NUMBER: 34-09283
TITLE: Needleless implant delivery of **gonadotropin releasing hormone** enhances the calving rate of beef cows synchronized with norgestomet and **estradiol valerate**
AUTHOR: Kesler, D. J.; Favero, R. J.
CORPORATE SOURCE: Dept. of Animal Sci., Univ. of Illinois, Urbana, IL 61801, USA Reprints: 1207 W. Gregory Dr., Urbana, IL 61801, USA
SOURCE: Drug Development and Industrial Pharmacy (USA), (1997) Vol.

CORPORATE NAME: Drug Manufacturer: Kade Pharmazeutische Fabrik, Germany; Serono, Switzerland; Schering AG, Germany

L169 ANSWER 23 OF 41 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1996:26158636 BIOTECHNO
TITLE: Premature progesterone elevation does not alter oocyte quality in in vitro fertilization
AUTHOR: Fanchin R.; Righini C.; Olivennes F.; De Ziegler D.; Selva J.; Frydman R.
CORPORATE SOURCE: Dept. of Obstetrics and Gynecology, Hopital Antoine Beclere, 157, rue de la Porte de Trivaux,92141, Clamart, France.
SOURCE: Fertility and Sterility, (1996), 65/6 (1178-1183)
CODEN: FESTAS ISSN: 0015-0282
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: Objective: To clarify whether premature P elevation during controlled ovarian hyperstimulation (COH) for IVF-ET affects adversely oocyte-embryo quality. Design: Controlled clinical study. Patients: We studied 102 fertile donors undergoing 106 oocyte retrievals and 117 recipients undergoing 162 ET. Interventions: Donors underwent COH with a time-release GnRH agonist and hMG. All recipients had inactive or absent ovaries and were primed with E.sub.2 and P. Main Outcome Measures: Measurement of LH, P, and E.sub.2; characteristics of COH; cleavage, pregnancy, and implantation rates. Results: According to donors' plasma P levels on the day of hCG, two groups were defined: P <= 0.9 ng/mL (conversion factor to SI unit, 3.18), group A, and P > 0.9 ng/mL, group B. Similar results of cleavage (65% and 72%), clinical (30% and 29%), and ongoing pregnancy (20% and 18%), and implantation (14% and 15%) rates were observed in both groups, respectively. Conclusions: The lack of difference in cleavage, pregnancy, and implantation rates between both groups suggests that preovulation increase in P production does not alter oocyte-embryo quality. Hence, the reported **adverse effects** on IVF outcome of pre-hCG elevation of P is likely to reflect an impaired endometrial receptivity in the high P group.
CONTROLLED TERM: *estradiol; ***gonadorelin** agonist; *human menopausal gonadotropin; *progesterone; *fertilization in vitro; *progesterone release; **estradiol valerate**; adult; article; female; hormonal regulation; human; human cell; human experiment; human tissue; implantation; normal human; oocyte maturation; ovary hyperstimulation; priority journal; treatment outcome
CAS REGISTRY NUMBER: (estradiol) 50-28-2; (human menopausal gonadotropin) 61489-71-2; (progesterone) 57-83-0; (**estradiol valerate**) **979-32-8**
CHEMICAL NAME: Drug Trade Name: progynova; utrogestan
CORPORATE NAME: Drug Manufacturer: schering, France; besins iscovesco, France; organon, France; takeda, France

L169 ANSWER 24 OF 41 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN

COUNTRY: Denmark
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: Subject. Luteal phase support has been shown in the past to be an essential part of ovarian stimulation protocols, especially the long protocol. It could be shown that hCG is as effective as is progesterone for luteal phase support but hCG is accompanied by a higher rate of complications. Methods. Progesterone can be administered in several routes. The oral, intramuscular (i.m.) and vaginal routes have been chosen frequently in the past. The oral route is ineffective, since progesterone has a low oral bioavailability (<10%), and a high rate of metabolites, which may result in **side effects** such as somnolence etc. Intramuscular administration provides very high serum levels of progesterone and this route is effective with regard to pregnancy rates. Injection of progesterone, however, is painful and cannot be done by the patient herself. The vaginal route is also effective, progesterone can be administered by the patient herself and progesterone is delivered directly to the uterus, where high levels are achieved (first uterine pass effect). Results. Several studies could show, in the past, that the vaginal administration of progesterone is effective also with regard to the downregulation of uterine contractions. Crinone® 8% Vaginal Gel is especially designed for vaginal use with a special applicator and has to be administered once daily in the morning. It adheres to the vaginal epithelium, and leakage of the gel is substiantially reduced as compared to other drugs like capsules or suppositories. Conclusions. Since progesterone is as effective as hCG for luteal phase support but provides a higher safety with regard to ovarian hyperstimulation syndromes, and vaginal progesterone is as effective as intramuscular progesterone, vaginal progesterone should be the standard choice for luteal phase support. Crinone® 8% seems to be the most comfortable way of vaginal administration of progesterone for luteal phase support in IVF cycles.
CONTROLLED TERM: *ovary hyperstimulation; *fertilization in vitro; *progesterone; *chorionic gonadotropin; luteal phase; drug efficacy; drug bioavailability; drug induced disease; somnolence; drug safety; first pass effect; uterus contraction; gel; human; female; major clinical study; clinical trial; randomized controlled trial; controlled study; adult; article; priority journal; estrogen; estradiol; **gonadorelin** agonist; **gonadorelin** antagonist; human menopausal gonadotropin; follitropin; clomifene citrate; utrogest; cetrorelix; gravibinan
CAS REGISTRY NUMBER: (progesterone) 57-83-0; (chorionic gonadotropin) 9002-61-3; (estradiol) 50-28-2; (human menopausal gonadotropin) 61489-71-2; (follitropin) 9002-68-0; (clomifene citrate) 50-41-9; (cetrorelix) 120287-85-6; (gravibinan) **65272-78-8**
CHEMICAL NAME: Drug Trade Name: utrogest; crinone; cetrotide; gravibinon

Searched by Barb O'Bryen, STIC 2-2518

of treatment that has become more established in Western medicine over the last decade. Discussed are the scientific documentation and aspects of acupuncture research, the physiological basis for the use of acupuncture, and evidence for the use of acupuncture in reproductive medicine. We are well aware that there are few well-designed papers on the effectiveness of different treatments in this field. However, we need to adhere to these principles, as we hope, do the readers of the present debate article.

CONTROLLED TERM: *acupuncture; *infertility therapy; human; clinical trial; nonhuman; safety; infertility; alternative medicine; evidence based medicine; health care cost; physician attitude; medical research; clinical protocol; methodology; needle; psychological aspect; comparative study; validation process; energy; peripheral nervous system function; electrostimulation; analgesia; sympathetic tone; stress; hypothalamus hypophysis adrenal system; sensory nerve; pain; spinal reflex; tranquilizing activity; sensory stimulation; pain threshold; pregnancy; **cardiovascular** effect; fertilization in vitro; embryo transfer; nidation; anesthesia; oocyte; ovary polycystic disease; disorders of hormone metabolism; anovulation; drug effect; review; opiate; oxytocin; beta endorphin; mu opiate receptor; corticotropin releasing factor; proopiomelanocortin; intermedin; **gonadorelin** ; gonadotropin; glutamic acid; aspartic acid; n methyl dextro aspartic acid receptor; substance P; vasoactive intestinal polypeptide; calcitonin gene related peptide; naloxone; cholecystokinin; alfentanil; anesthetic agent; **estradiol valerate**

CAS REGISTRY NUMBER: (opiate) 53663-61-9, 8002-76-4, 8008-60-4; (oxytocin) 50-56-6, 54577-94-5; (beta endorphin) 59887-17-1; (corticotropin releasing factor) 9015-71-8; (proopiomelanocortin) 66796-54-1; (intermedin) 9002-79-3, 9046-72-4; (**gonadorelin**) 33515-09-2, **9034-40-6**; (gonadotropin) 63231-54-9; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0, 6899-05-4; (aspartic acid) 56-84-8, 6899-03-2; (substance P) 33507-63-0; (vasoactive intestinal polypeptide) 37221-79-7; (calcitonin gene related peptide) 83652-28-2; (naloxone) 357-08-4, 465-65-6; (cholecystokinin) 9011-97-6, 93443-27-7; (alfentanil) 69049-06-5, 71195-58-9; (**estradiol valerate**) **979-32-8**

L169 ANSWER 22 OF 41 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2001:32473055 BIOTECHNO

TITLE: Evaluation of an optimal luteal phase support protocol in IVF

AUTHOR: Ludwig M.; Diedrich K.

CORPORATE SOURCE: Dr. M. Ludwig, Klin. Frauenheilkunde/Geburtshilfe, Universitatsklinikum Lubeck, Ratzeburger Allee 160, 23538 Lubeck, Germany.

SOURCE: Acta Obstetricia et Gynecologica Scandinavica, (2001), 80/5 (452-466), 65 reference(s)
CODEN: AOGSAE ISSN: 0001-6349

DOCUMENT TYPE: Journal; Article

Searched by Barb O'Bryen, STIC 2-2518

CONTROLLED TERM: *uterus myoma; general practitioner; risk factor; menarche; obesity; nullipara; ethnic difference; incidence; disease severity; symptomatology; tumor volume; tumor localization; clinical examination; echography; transvaginal echography; nuclear magnetic resonance imaging; computer assisted tomography; ovary tumor; hysteroscopy; laparoscopic surgery; myomectomy; hysterectomy; uterine artery embolization; endoscopic surgery; safety; drug mechanism; **hot flush**; osteoporosis; gene therapy; human; female; review; **gonadorelin** agonist; goserelin; estriol; **estradiol valerate**; estradiol; mifepristone; interferon; selective estrogen receptor modulator; tamoxifen; raloxifene; cytotoxic agent; menorest 75

CAS REGISTRY NUMBER: (goserelin) 65807-02-5; (estriol) 50-27-1; (**estradiol valerate**) **979-32-8**; (estradiol) 50-28-2; (mifepristone) 84371-65-3; (tamoxifen) 10540-29-1; (raloxifene) 82640-04-8, 84449-90-1

CHEMICAL NAME: Drug Trade Name: zoladex; ru 486; ovestin; progynova; menorest 75

L169 ANSWER 21 OF 41 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2002:34904784 BIOTECHNO

TITLE: Alternative treatments in reproductive medicine: Much ado about nothing: Acupuncture - A method of treatment in reproductive medicine: Lack of evidence of an effect does not equal evidence of the lack of an effect

AUTHOR: Stener-Victorin E.; Wikland M.; Waldenstrom U.; Lundeberg T.

CORPORATE SOURCE: E. Stener-Victorin, Dept. of Obstetrics and Gynaecology, Goteborg University, SE-413 45 Goteborg, Sweden.
E-mail: elisabet.stener-victorin@medstud.gu.se

SOURCE: Human Reproduction, (2002), 17/8 (1942-1946), 47 reference(s)
CODEN: HUREEE ISSN: 0268-1161

DOCUMENT TYPE: Journal; General Review

COUNTRY: United Kingdom

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: The increasing popularity of alternative treatments - methods of treatment that are not generally established in Western medicine - demands a serious debate about scientific documentation, efficacy and safety. It has been argued that there is no alternative medicine. There is only scientifically proven, evidence-based medicine supported by solid data, and we agree. Different methods of treatment, referred to as alternative treatments, are used by millions of patients every day which generates billions of dollars in health care expenditure each year. Therefore, it is important that physicians become more knowledgeable about different methods of treatment and increase their understanding of the possible benefits and limitations of each therapy. This article is intended to illustrate acupuncture in reproductive medicine today, as an example of a method

AE; GOSERELIN *RN; S.C. *FT; IMPLANT *FT; LULIBERIN-AGONIST *FT; MODE-OF-ACT. *FT; ZENECA *FT; INJECTION *FT; **RELEASING-FACTOR** *FT; **RELEASING-FACTORS** *FT; LULIBERIN-AGONISTS *FT; TR *FT; **AE** *FT

CAS REGISTRY NO.: 65807-02-5
[02] **ESTRADIOL-VALERATE** *TR; ESTRADIOL-VALERATE * **AE**; DIVINA *TR; DIVINA ***AE**; ORION *FT; HYPOESTROGENIC *TR; VASOMOTOR *TR; **FLUSHING** *TR; SWEATING *TR; LIBIDO *TR; BREAKTHROUGH-BLEEDING ***AE** ; HEADACHE ***AE**; PREMENSTRUAL-TENSION ***AE**; SWEAT *TR; MENSTRUATION ***AE**; GYNECOLOGY ***AE** ; MENTAL-DISORDER ***AE**; MENSTRUATION ***AE**; ESTRADIOV *RN; COMB.PREP. *FT; ESTROGEN *FT; ESTROGENS *FT; TR *FT; **AE** *FT

CAS REGISTRY NO.: **979-32-8**
[03] MEDROXYPROGESTERONE-ACETATE *TR; MEDROXYPROGESTERONE-ACETATE ***AE**; DIVINA**TR; DIVINA ***AE**; ORION *FT; HYPOESTROGENIC *TR; VASOMOTOR *TR; **FLUSHING** *TR; SWEATING *TR; LIBIDO *TR; BREAKTHROUGH-BLEEDING ***AE** ; HEADACHE ***AE**; PREMENSTRUAL-TENSION ***AE**; SWEAT *TR; MENSTRUATION ***AE**; GYNECOLOGY ***AE** ; MENTAL-DISORDER ***AE**; MENSTRUATION ***AE**; MEDOXPRAC *RN; COMB.PREP. *FT; PROGESTOGEN *FT; PROGESTOGENS *FT; TR *FT; **AE** *FT

CAS REGISTRY NO.: 71-58-9
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L169 ANSWER 20 OF 41 BIOTECHNO COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2003:36267579 BIOTECHNO
TITLE: Uterine fibroids an update for GPs
AUTHOR: Jones I.
CORPORATE SOURCE: Prof. I. Jones, University of Queensland, Mater Mothers' Hospital, Brisbane, QLD, Australia.
SOURCE: Medicine Today, (01 FEB 2003), 4/2 (16-20), 1 reference(s)
CODEN: MTNBCV ISSN: 1443-430X
DOCUMENT TYPE: Journal; General Review
COUNTRY: Australia
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: .bullet. Risk factors for the development of uterine fibroids include an early menarche, obesity, nulliparity and being of Africa origin. .bullet. The incidence and severity of a woman's symptons depend on the size, number and anatomical location of the fibroids in the uterus. .bullet. Diagnosis of uterine fibroids is by clinical examination, pelvic ultrasound examination (including vaginal ultrasound with or without saline infusion sonography), MRI and CT scan. .bullet. Beware the postmenopausal fibroid - it be an ovaian tomour. .bullet. Management options for symptomatics fibroids include hysteroscopic submucous fibroid resection, laparoscopic and open myomectomy, laparoscopic or open hysterectomy and in some cases uterine artery embolisation. .bullet. The use of GnRH agonists to shrink the size of fibroid before surgery has made both open and endoscopic treatment easier and safer.

23, pp. 607-610. 15 Refs.
CODEN: DDIPD8; ISSN: 0363-9045.
DOCUMENT TYPE: Journal
LANGUAGE: English
ABSTRACT:

One-hundred and six beef cows were included in a study to determine if ***gonadorelin*** (**gonadotropin releasing hormone**) administered via needleless implants would enhance calving rate like conventional **gonadorelin** administration; all cows were synchronized with the norgestomet and **estradiol valerate** estrus synchronization procedure and then randomly assigned to 1 of 3 groups: no ***gonadorelin*** , **gonadorelin** via conventional implants, and ***gonadorelin*** via needleless implants.

Gonadorelin was administered 30 h after norgestomet implant removal. Needleless implants were administered while cows were restrained. ***Gonadorelin*** administered by both methods equally enhanced calving rate and the needleless implant caused minimal response by the cows.

It was concluded that remote administration of **gonadorelin** may accomplish therapeutic efficacy and reduce the time, labor, stress, and risk of injury associated with providing conventional animal therapy.

M. Therese Gyi
SECTION: 8 Biopharmaceutics; 12 Preliminary Drug Test
CLASSIFICATION: 68:00 Hormones
INDEX TERM: **Gonadorelin**; implants; cows
INDEX TERM: Norgestomet; concomitant therapy
INDEX TERM: **Estradiol valerate**; concomitant therapy
INDEX TERM: Hormones; **gonadorelin**; implants
INDEX TERM: Implants; **gonadorelin**; administration
INDEX TERM: Drug administration; **gonadorelin**; implants
INDEX TERM: Dosage forms; **gonadorelin**; implants
INDEX TERM: Drug administration routes; subdermal; **gonadorelin**
CAS REGISTRY NO.: **33515-09-2 (Gonadorelin)**
CAS REGISTRY NO.: 25092-41-5 (Norgestomet)
CAS REGISTRY NO.: **979-32-8 (Estradiol valerate)**
CHEMICAL NAME: **Gonadorelin (Gonadotropin releasing hormone)**

L169 ANSWER 26 OF 41 IPA COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 84:10285 IPA
DOCUMENT NUMBER: 23-03355
TITLE: Growth and sexual development before and after sex steroid therapy in patients with thalassemia major
AUTHOR: Landau, H.; Gross, V.; Dagan, I.; Palti, Z.; Spitz, I. M.; et al
CORPORATE SOURCE: Dept. of Endocrinology and Metabolism, Shaare Zedek Med. Ctr., Jerusalem, Israel
SOURCE: Archives of Internal Medicine (USA), (Dec 1984) Vol. 144, pp. 2341-2346. 19 Refs.
CODEN: AIMDAP; ISSN: 0003-9926.
DOCUMENT TYPE: Journal
FILE SEGMENT: HUMAN
LANGUAGE: English
ABSTRACT:

The effect of sex steroid therapy on growth and sexual development of patients with thalassemia major was studied in 5 female patients (older than 18 yr) treated with low dose Progyluton (estradiol, combination, **estradiol** ***valerate*** , norgestrel) or Microgynon (ethinyl estradiol, combination, levonorgestrel), 9 female patients (younger than 18 yr) treated with ***gonadorelin*** (**gonadotropin releasing hormone**) given as an oral tablet, and 9 male patients (younger than 19 yr) treated

with long acting Durasteron (testosterone enanthate, combination, testosterone propionate, testosterone undecylenate) injection.

The results showed that 4 of the females treated with estrogen-progesterone preparation and 6 of the males treated with testosterone preparations showed satisfactory pubertal progression.

It was concluded that treatment with sex steroids should be considered in both female and male patients with thalassemia major.

Elvira deC. Weiss

SECTION: 6 Drug Evaluations
CLASSIFICATION: 68:00 Hormones; 68:00 Hormones; 68:00 Hormones; 68:00 Hormones
INDEX TERM: Estradiol; combination, **estradiol valerate**, norgestrel; puberty, thalassemia major
INDEX TERM: **Estradiol valerate**; combination, estradiol, norgestrel; puberty, thalassemia major
INDEX TERM: Norgestrel; combination, estradiol, **estradiol valerate**; puberty, thalassemia major
INDEX TERM: Ethinyl estradiol; combination, levonorgestrel; puberty, thalassemia major
INDEX TERM: Levonorgestrel; combination, ethinyl estradiol; puberty, thalassemia major
INDEX TERM: **Gonadorelin**; effects; puberty, lack, thalassemia major
INDEX TERM: Testosterone enanthate; combination, testosterone propionate, testosterone undecylenate; puberty, thalassemia major
INDEX TERM: Testosterone propionate; combination, testosterone enanthate, testosterone undecylenate; puberty, thalassemia major
INDEX TERM: Testosterone undecylenate; combination, testosterone enanthate, testosterone propionate; puberty, thalassemia major
INDEX TERM: Puberty; estradiol, combination, **estradiol valerate**, norgestrel; thalassemia major
INDEX TERM: Puberty; ethinyl estradiol, combination, levonorgestrel; thalassemia major
INDEX TERM: Puberty; testosterone enanthate, combination, testosterone propionate, testosterone undecylenate; thalassemia major
INDEX TERM: Puberty; **gonadorelin**; thalassemia major
INDEX TERM: Thalassemia; estradiol, combination, **estradiol valerate**, norgestrel; effects, puberty
INDEX TERM: Thalassemia; ethinyl estradiol, combination, levonorgestrel; effects, puberty
INDEX TERM: Thalassemia; testosterone enanthate, combination, testosterone propionate, testosterone undecylenate; effects, puberty
INDEX TERM: Thalassemia; **gonadorelin**; effects, puberty
INDEX TERM: Hormones; **gonadorelin**; puberty, thalassemia major
INDEX TERM: Hormones; estradiol, combination, **estradiol valerate**, norgestrel; puberty, thalassemia major
INDEX TERM: Hormones; ethinyl estradiol, combination, levonorgestrel; puberty, thalassemia major
INDEX TERM: Hormones; testosterone enanthate, combination, testosterone propionate, testosterone undecylenate; puberty, thalassemia major
CAS REGISTRY NO.: 50-28-2 (Estradiol)
CAS REGISTRY NO.: **979-32-8 (Estradiol valerate)**
CAS REGISTRY NO.: 6533-00-2 (Norgestrel)
CAS REGISTRY NO.: 57-63-6 (Ethinyl estradiol)
CAS REGISTRY NO.: 797-63-7 (Levonorgestrel)

CAS REGISTRY NO.: **33515-09-2 (Gonadorelin)**
CAS REGISTRY NO.: 315-37-7 (Testosterone enanthate)
CAS REGISTRY NO.: 57-85-2 (Testosterone propionate)
CHEMICAL NAME: Testosterone undecylenate
CHEMICAL NAME: **Gonadorelin, combination, estradiol valerate, norgestrel, combination, levonorgestrel, combination, testosterone propionate, testosterone undecylenate (Gonadotropin releasing hormone); Estradiol, combination, estradiol valerate, norgestrel, combination, levonorgestrel, combination, testosterone propionate, testosterone undecylenate (Progyluton)**; Ethinyl estradiol, combination, levonorgestrel, combination, testosterone propionate, testosterone undecylenate (Microgynon); Testosterone enanthate, combination, testosterone propionate, testosterone undecylenate (Durasteron)

L169 ANSWER 27 OF 41 IPA COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 81:7560 IPA
DOCUMENT NUMBER: 20-04450
TITLE: Danazol: endocrine consequences in healthy women
AUTHOR: Luciano, A. A.; Hauser, K. S.; Chapler, F. K.; Sherman, B. M.
CORPORATE SOURCE: Div. of Reproductive Endocrinology, Dept. of Obstet. and Gynecol., Univ. of Iowa, Iowa City, IA 52242
SOURCE: American Journal of Obstetrics and Gynecology (USA), (Nov 15 1981) Vol. 141, pp. 723-727. 19 Refs.
CODEN: AJOGAH; ISSN: 0002-9378.
DOCUMENT TYPE: Journal
FILE SEGMENT: HUMAN
LANGUAGE: English
ABSTRACT:

The effects of danazol (I) on pituitary and gonadal functions were studied in 7 normal women (aged 24-40 yr) given oral I, at a dose of 400 mg 2 times/day, for 2 months.

Circulating levels of sex steroids, gonadotropins, and prolactin on alternate days throughout a control menstrual cycle and during treatment were measured. Danazol inhibited ovulation in all subjects. The amenorrheic state induced by I was characterized by normal basal levels of gonadotropins, prolactin, and estrogen. Serum androgen levels were significantly increased as was the urinary excretion of 17-ketosteroids. The LH and FSH responses to ***gonadotropin*** **-releasing hormone** were enhanced during treatment, and there was a normal LH rise following administration of ***estradiol*** **valerate**, indicative of intact positive feedback. These observations fail to support the contention that I suppresses pituitary gonadotropin secretion or directly inhibits steroidogenesis.

It was concluded that I may have a primary site of action at the ovary by suppressing the normal, orderly process of follicular maturation.
Elvira deC. Weiss

SECTION: 11 Pharmacology
CLASSIFICATION: 68:08 Androgens
INDEX TERM: Danazol; effects; pituitary, and gonadal functions, mechanisms, humans
INDEX TERM: Mechanism of action; danazol; effects, pituitary and gonadal functions, humans
INDEX TERM: Androgens; danazol; effects, pituitary and gonadal functions, mechanisms, humans
INDEX TERM: Site of action; danazol; ovary, humans
CAS REGISTRY NO.: 17230-88-5 (Danazol)

L169 ANSWER 28 OF 41 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:145920 BIOSIS
DOCUMENT NUMBER: PREV200600135910
TITLE: Endocrine treatment of male-to-female transsexuals using **gonadotropin-releasing hormone** agonist.
AUTHOR(S): Dittrich, R.; Binder, H.; Cupisti, S.; Hoffmann, I.; Beckmann, M. W.; Mueller, A. [Reprint Author]
CORPORATE SOURCE: Erlangen Univ Hosp, Dept Obstet and Gynaecol, Univ Str 21-23, D-91054 Erlangen, Germany andreas.mueller@gyn.imed.uni-erlangen.de
SOURCE: Experimental and Clinical Endocrinology & Diabetes, (DEC 2005) Vol. 113, No. 10, pp. 586-592. ISSN: 0947-7349.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Feb 2006
Last Updated on STN: 22 Feb 2006

ABSTRACT:in transsexual people; cross-sex hormone therapy is an important component of medical treatment. In male-to-female transsexuals, feminizing effects should be achieved before irreversible sex reassignment surgery (SRS) is considered. The most common treatment regimen in male-to-female transsexuals is a combination of ethinyl oestradiol and cyproterone acetate, with the exception of transdermal oestradiol-17 beta in individuals over the age of 40. The mortality and morbidity rates with this treatment regimen have been reported in more than 800 patients. Typical **side** ***effects*** include venous thrombosis, elevated liver enzymes, symptomatic gallstones, hyperprolactinaemia and **depression.** Sixty male-to-female transsexuals were treated with monthly injections of **gonadotropin-releasing** ***hormone*** agonist (GnRHa) and oral oestradiol-17 beta valerate for 2 years to achieve feminisation until SRS. There was a significant decline in gonadotropins, total testosterone and calculated free testosterone. In general, the treatment regimen was well accepted. An equal increase in breast size was achieved compared to common hormone therapy. Two ***side*** **effects** were documented. One, venous thrombosis, occurred in a patient with a homozygous MTHFR mutation. One patient was found to be suffering from symptomatic preexisting gallstones. No other complications were documented. Liver enzymes, lipids, and prolactin levels were unchanged. Significantly increased oestradiol and SHBG serum levels were detectable. In addition, an increase in bone mass density, in the femoral neck and lumbar spine, was recorded. We conclude that cross-sex hormone treatment of male-to-female transsexuals using GnRHa and oestradiol-17 beta valerate is ***effective*** , and **side effects** and complication rates can be reduced using the treatment regimen presented here.

CONCEPT CODE: Genetics - Human 03508
Pathology - Therapy 12512
Urinary system - Pathology 15506
Reproductive system - Pathology 16506
Endocrine - General 17002
Nervous system - Physiology and biochemistry 20504
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
Toxicology - Pharmacology 22504

INDEX TERMS: Major Concepts
Pharmacology; Urology (Human Medicine, Medical Sciences); Gynecology (Human Medicine, Medical Sciences); Clinical Endocrinology (Human Medicine,

Medical Sciences)
INDEX TERMS: Parts, Structures, & Systems of Organisms
lumbar spine: nervous system
INDEX TERMS: Chemicals & Biochemicals
liver enzyme; SHBG; cyproterone acetate: hormone-drug; ethinyl estradiol: hormone-drug, estrogen-drug; **gonadotropin-releasing hormone** agonist: hormone-drug, **adverse effects**, drug regimen, efficacy; estradiol-17-beta-valerate: hormone-drug, estrogen-drug, **adverse effects**, drug regimen, efficacy
INDEX TERMS: Methods & Equipment
cross-sex hormone therapy: therapeutic and prophylactic techniques, clinical techniques
INDEX TERMS: Miscellaneous Descriptors
morbidity rate; mortality rate; male-to-female transsexual
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): female, male
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: 427-51-0 (cyproterone acetate)
57-63-6 (ethinyl estradiol)
979-32-8 (estradiol-17-beta-valerate)
GENE NAME: human MTHFR gene (Hominidae)

L169 ANSWER 29 OF 41 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:397525 BIOSIS
DOCUMENT NUMBER: PREV199598411825
TITLE: Long oestradiol replacement in an oocyte donation programme.
AUTHOR(S): Remohi, Jose; Gutierrez, Antonio; Cano, Fidel; Ruiz, Amparo; Simon, Carlos; Pellicer, Antonio [Reprint author]
CORPORATE SOURCE: Instituto Valenciano de Infertilidad, Guardia Civil 23, 46020 Valencia, Spain
SOURCE: Human Reproduction (Oxford), (1995) Vol. 10, No. 6, pp. 1387-1391.
CODEN: HUREEE. ISSN: 0268-1161.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Sep 1995
Last Updated on STN: 13 Sep 1995
ABSTRACT:The objective of this study was to optimize, in terms of endometrial receptivity (embryo implantation), the limits of unopposed administration of oestrogens beyond 35 days in an in-vitro fertilization (IVF) and ovum donation programme. Oocytes donated by 182 women undergoing IVF were distributed among 186 women treated by ovum donation. Five groups of recipients were established according to the duration of oestradiol valerate administration, in a 'prolonged follicular phase' protocol, before embryo replacement, employing oestradiol valerate at increasing doses up to 6 mg/day. Gonadotrophin-releasing hormone analogues (GnRHa) were simultaneously administered in ovulatory patients. The dosage of oestradiol valerate was maintained until oocytes were available for insemination and subsequent transfer. Donors and recipients were equally distributed among groups in terms of age and cause of

infertility. There was no difference among groups in serum oestradiol concentration the day in which progesterone was added to obtain a secretory transformation of the endometrium. An analysis of the ovum donation cycles showed no difference among groups in pregnancy and implantation rates after the replacement of a similar number of embryos. Successful implantation was observed even after 100 days of unopposed oestradiol valerate administration. Break-through bleeding increasingly appeared according to the duration of oestrogen replacement. These clinical observations provide evidence that the concept of 'prolonged follicular phase' oestrogen replacement for ovum donation can be maintained, at least as long as 15 weeks. However, because of the high (gt 44%) incidence of break-through bleeding after 9 weeks, it is advisable to stop oestrogen treatment at this point. This protocol enormously facilitates the chances of synchronization between donor and recipient in an anonymous oocyte donation programme.

CONCEPT CODE: Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Sterols and steroids 10067
Pathology - Therapy 12512
Cardiovascular system - Blood vessel pathology 14508
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Endocrine - Gonads and placenta 17006
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
Pharmacology - Reproductive system and implantation studies 22028
In vitro cellular and subcellular studies 32600

INDEX TERMS: Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination); Pharmacology; Reproductive System (Reproduction)

INDEX TERMS: Chemicals & Biochemicals
OESTRADIOL; ESTRADIOL VALERATE; PROGESTERONE

INDEX TERMS: Miscellaneous Descriptors
BREAK-THROUGH BLEEDING; ENDOMETRIAL RECEPTIVITY; ESTRADIOL VALERATE; **GONADOTROPIN-RELEASING HORMONE** ANALOG; HORMONE-DRUG; IN-VITRO FERTILIZATION; INFERTILITY; OOCYTE DONATION PROGRAM; PREGNANCY; PROGESTERONE

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: 50-28-2 (OESTRADIOL)
979-32-8 (ESTRADIOL VALERATE)
57-83-0 (PROGESTERONE)

L169 ANSWER 30 OF 41 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1982:203875 BIOSIS

DOCUMENT NUMBER: PREV198273063859; BA73:63859
TITLE: DANAZOL ENDOCRINE CONSEQUENCES IN HEALTHY WOMEN.
AUTHOR(S): LUCIANO A A [Reprint author]; HAUSER K S; CHAPLER F K; SHERMAN B M
CORPORATE SOURCE: DIV OF REPRODUCTIVE ENDOCRINOLOGY, DEP OF OBSTETRICS AND GYNECOL, UNIV OF IOWA, IOWA CITY, IOWA 52242, USA
SOURCE: American Journal of Obstetrics and Gynecology, (1981) Vol. 41, No. 6, pp. 723-727.
CODEN: AJOGAH. ISSN: 0002-9378.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ABSTRACT:The effects of danazol on pituitary and gonadal function was studied in 7 normal women who volunteered to take danazol, 400 mg twice daily, for 2 mo. Circulating sex steroids, gonadotropins and prolactin levels were measured on alternate days throughout a control menstrual cycle and during treatment. Danazol inhibited ovulation in all subjects. The amenorrheic state induced by danazol was characterized by normal basal levels on gonadotropins, prolactin and estrogen. Serum androgen levels were significantly increased as was the urinary excretion of 17-ketosteroids. The LH [luteinizing hormone] and FSH responses to **gonadotropin-releasing hormone** were enhanced during treatment, and there was a normal LH rise following administration of estradiol valerate, indicative of intact positive feedback. These observations fail to support the contention that danazol suppresses pituitary gonadotropin secretion or directly inhibits steroidogenesis. Danazol may have a primary site of action at the ovary by suppressing the normal, orderly process of follicular maturation. [Danazol, a synthetic isoxazol derivative of 17-α ethinyl testosterone, was introduced for the treatment of endometriosis. Since then, danazol has been found to be useful in the therapy of benign fibrocystic disease of the breast, precocious puberty, congenital angioneurotic edema, and as a contraceptive in men and women.].
CONCEPT CODE:
Genetics - Human 03508
Clinical biochemistry - General methods and applications 10006
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Sterols and steroids 10067
Biochemistry studies - Carbohydrates 10068
Enzymes - Physiological studies 10808
Pathology - Comparative 12503
Pathology - Inflammation and inflammatory disease 12508
Pathology - Therapy 12512
Metabolism - Sterols and steroids 13008
Metabolism - Metabolic disorders 13020
Blood - Other body fluids 15010
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Endocrine - Gonads and placenta 17006
Endocrine - Pituitary 17014
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Pharmacology - Endocrine system 22016
Pharmacology - Immunological processes and allergy 22018
Pharmacology - Reproductive system and implantation studies 22028
Pediatrics - 25000
Development and Embryology - Pathology 25503

Development and Embryology - Morphogenesis 25508
Immunology - Immunopathology, tissue immunology 34508

INDEX TERMS: Major Concepts
Clinical Chemistry (Allied Medical Sciences); Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Pharmacology; Reproductive System (Reproduction)

INDEX TERMS: Miscellaneous Descriptors
ESTRADIOL VALERATE CONTRACEPTIVE-DRUG **GONADOTROPIN RELEASING HORMONE** HORMONE-DRUG FSH LUTEINIZING HORMONE GONADOTROPINS SEX STEROIDS ENDOMETRIOSIS PRECOCIOUS PUBERTY BENIGN FIBRO CYSTIC DISEASE CONGENITAL ANGIO NEUROTIC EDEMA PHARMACODYNAMICS FOLLICULAR MATURATION **DEPRESSION**

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

REGISTRY NUMBER: 17230-88-5 (DANAZOL)
979-32-8 (ESTRADIOL VALERATE)
9002-68-0 (FSH)
9002-67-9 (LUTEINIZING HORMONE)
33515-09-2Q (**GONADOTROPIN RELEASING HORMONE**)
107950-52-7Q (**GONADOTROPIN RELEASING HORMONE**)

L169 ANSWER 31 OF 41 EMBASE

ACCESSION NUMBER: 2004220561 EMBASE
TITLE: Oestrogen and attacks of migraine with and without aura.
AUTHOR: MacGregor E.A.
CORPORATE SOURCE: E.A. MacGregor, City of London Migraine Clinic, 22 Charterhouse Square, London, EC1M 6DX, United Kingdom. anne.macgregor@bartsandthelondon.nhs.uk
SOURCE: Lancet Neurology, (1 Jun 2004) Vol. 3, No. 6, pp. 354-361.
.
Refs: 67
ISSN: 1474-4422 CODEN: LNAEAM
PUBLISHER IDENT.: S 1474-4422(04)00768-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040701
Last Updated on STN: 20040701

ABSTRACT: During women's reproductive years, migraine is three times more common than in men of a similar age. Although this female preponderance is commonly assumed to be associated with the additional trigger of fluctuating sex hormones of the menstrual cycle, few studies have been done to confirm or

refute this. This review is confined to the relation between oestrogen and attacks of migraine. The evidence for an association between oestrogen "withdrawal" and attacks of migraine without aura is presented, as well as evidence for an association between high oestrogen states and attacks of migraine with aura. Only clinical data are presented here.

CONTROLLED TERM: Medical Descriptors:
*migraine: CO, complication
*migraine: DT, drug therapy
*migraine: ET, etiology
***migraine: SI, side effect**
*hallucination
disease association
drug withdrawal
menstruation
menstrual cycle
ovulation
hormonal therapy
follicular phase
luteal phase
bleeding: SI, side effect
hormone substitution
ovariectomy
device
gel
drug exposure
drug efficacy
estrogen deficiency: SI, side effect
hot flush: SI, side effect
bone density
side effect: SI, side effect
drug use
disease exacerbation: SI, side effect
stroke: SI, side effect
cerebrovascular accident: SI, side effect
cardiovascular risk
risk factor
human
clinical trial
review
priority journal
Drug Descriptors:
*estrogen: AE, adverse drug reaction
*estrogen: CT, clinical trial
*estrogen: CB, drug combination
*estrogen: CM, drug comparison
*estrogen: DT, drug therapy
*estrogen: PR, pharmaceutics
progesterone: DT, drug therapy
estradiol valerate: DT, drug therapy
estradiol valerate: IM, intramuscular drug administration
estradiol: AD, drug administration
estradiol: PO, oral drug administration
gonadorelin: AE, adverse drug reaction
gestagen: CB, drug combination
oral contraceptive agent: AE, adverse drug reaction
oral contraceptive agent: PO, oral drug administration
medroxyprogesterone acetate: AE, adverse drug reaction

CAS REGISTRY NO.: (progesterone) 57-83-0; (estradiol valerate)

979-32-8; (estradiol) 50-28-2; (gonadorelin) 33515-09-2, 9034-40-6; (medroxyprogesterone acetate) 71-58-9
NAME OF PRODUCT: Clearplan

L169 ANSWER 32 OF 41 EMBASE
ACCESSION NUMBER: 2004151204 EMBASE
TITLE: Applications of chemically-modified cyclodextrins: Use of hydroxypropyl-β-cyclodextrin as an enabling excipient for brain targeting, redox-based derivatives of estradiol: A review of preclinical and clinical findings.
AUTHOR: Brewster M.E.; Loftsson T.; Bodor N.
CORPORATE SOURCE: M.E. Brewster, Dept. of Pharmaceutical Sciences, J./Johnson Pharmaceut. Res./Devmt., Beerse, Belgium. mbrewste@prdbe.jnj.com
SOURCE: Journal of Drug Delivery Science and Technology, (2004) Vol. 14, No. 1, pp. 21-34. .
Refs: 96
ISSN: 1157-1489 CODEN: JDDSAL
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040513
Last Updated on STN: 20040513

ABSTRACT: Estrogen depletion associated with the menopause produces a constellation of debilitating symptoms which range the gamut from vasomotor complaints which severely affect over one-third of all climacteric women to cognitive deficits. While many of these complications can be alleviated with traditional hormone replacement therapy (HRT), fear of cancer, cardiovascular problems and other metabolic diseases prompt many women to avoid treatment. Surveys suggest that over 30% of all prescriptions written for HRT are never filled due to these concerns and recent findings from Woman's Health Initiative trials have only added to these trepidations. Selective brain delivery of estrogens, in general, and estradiol, in particular, may address these items. One approach to accomplish CNS deposition is the use of a chemical delivery system for estradiol that selectively targets the central nervous system and may, therefore, reduce the incidence or severity of peripherally manifested side-effects. Owing to the very poor water solubility and limited stability of these derivatives, hydroxypropyl-β-cyclodextrin has proved to be enabling excipients in the development of these drug candidates. Various preclinical evaluations have demonstrated the organ-targeting potential of an estradiol-chemical delivery systems (E2-CDS) and therefore its potential usefulness as a therapeutic adjunct in certain subpopulations of menopausal women including those at risk to breast carcinomas. A very exciting potential use of the E2-CDS is in neurodegenerative diseases. Data suggest that estrogens may improve the mental performance of elderly patents suspected of having Alzheimer's disease.

CONTROLLED TERM: Medical Descriptors:
*chemical modification
*drug targeting
*brain
*oxidation reduction reaction

menopause
menopausal syndrome: DI, diagnosis
menopausal syndrome: DT, drug therapy
menopausal syndrome: ET, etiology
estrogen therapy
breast carcinoma: SI, side effect
cardiovascular disease: SI, side effect
metabolic disorder: SI, side effect
clinical trial
Woman Health Initiative
drug delivery system
chemical delivery system
solubility
molecular stability
degenerative disease: DI, diagnosis
degenerative disease: DT, drug therapy
Alzheimer disease: DI, diagnosis
Alzheimer disease: DT, drug therapy
drug effect
treatment indication
drug formulation
in vitro study
drug half life
drug distribution
drug release
area under the curve
drug brain level
drug elimination
mean residence time
drug protein binding
luteinizing hormone release
gonadorelin release
dose response
drug synthesis
sexual behavior
drug solubility
body weight
human
nonhuman
male
female
review
Drug Descriptors:
*cyclodextrin derivative
*2 hydroxypropyl beta cyclodextrin
*excipient
*estradiol: AE, adverse drug reaction
*estradiol: CT, clinical trial
*estradiol: AD, drug administration
*estradiol: CR, drug concentration
*estradiol: DO, drug dose
*estradiol: DT, drug therapy
***estradiol: TO, drug toxicity**
*estradiol: PR, pharmaceutics
*estradiol: PK, pharmacokinetics
*estradiol: PD, pharmacology
*estradiol: BD, buccal drug administration
*estradiol: IV, intravenous drug administration
*estradiol: PO, oral drug administration
*estradiol: RC, rectal drug administration

***estradiol: TD, transdermal drug administration**
estrogen: AE, adverse drug reaction
estrogen: CT, clinical trial
estrogen: DO, drug dose
estrogen: DT, drug therapy
estrogen: PR, pharmaceutics
estrogen: PK, pharmacokinetics
estrogen: PD, pharmacology
estrogen: BD, buccal drug administration
estrogen: IV, intravenous drug administration
estrogen: PO, oral drug administration
estrogen: RC, rectal drug administration
estrogen: TD, transdermal drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: AD, drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: DV, drug development
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: DO, drug dose
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: TO, drug toxicity
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: PR, pharmaceutics
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: PK, pharmacokinetics
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: PD, pharmacology
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: BD, buccal drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: IV, intravenous drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: PO, oral drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: RC, rectal drug administration
3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridin 3 yl)carbonyl]oxy]estra 1,3,5(10) triene: TD, transdermal drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: AD, drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: DV, drug development
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: DO, drug dose
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: TO, drug toxicity
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: PR, pharmaceutics
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: PK, pharmacokinetics
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: PD, pharmacology
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta

yl]oxy]carbonyl]pyridinium iodide: BD, buccal drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: IV, intravenous drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: PO, oral drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: RC, rectal drug administration
1 methyl 3 [[[3 hydroxyestra 1,3,5(10)trien 17beta yl]oxy]carbonyl]pyridinium iodide: TD, transdermal drug administration
estradiol nicotinate: AD, drug administration
estradiol nicotinate: DV, drug development
estradiol nicotinate: DO, drug dose
estradiol nicotinate: TO, drug toxicity
estradiol nicotinate: PR, pharmaceutics
estradiol nicotinate: PK, pharmacokinetics
estradiol nicotinate: PD, pharmacology
estradiol nicotinate: BD, buccal drug administration
estradiol nicotinate: IV, intravenous drug administration
estradiol nicotinate: PO, oral drug administration
estradiol nicotinate: RC, rectal drug administration
estradiol nicotinate: TD, transdermal drug administration
estradiol bisnicotinate: AD, drug administration
estradiol bisnicotinate: DV, drug development
estradiol bisnicotinate: DO, drug dose
estradiol bisnicotinate: TO, drug toxicity

CONTROLLED TERM: Drug Descriptors:
estradiol bisnicotinate: PR, pharmaceutics
estradiol bisnicotinate: PK, pharmacokinetics
estradiol bisnicotinate: PD, pharmacology
estradiol bisnicotinate: BD, buccal drug administration
estradiol bisnicotinate: IV, intravenous drug administration
estradiol bisnicotinate: PO, oral drug administration
estradiol bisnicotinate: RC, rectal drug administration
estradiol bisnicotinate: TD, transdermal drug administration
luteinizing hormone
gonadorelin
testosterone
androgen
prolactin
growth hormone
liothyronine
drug vehicle
unclassified drug
estradiol valerate

CAS REGISTRY NO.: (2 hydroxypropyl beta cyclodextrin) 94035-02-6; (estradiol) 50-28-2; (luteinizing hormone) 39341-83-8, 9002-67-9; (gonadorelin) 33515-09-2, 9034-40-6; (testosterone) 58-22-0; (prolactin) 12585-34-1, 50647-00-2, 9002-62-4; (growth hormone) 36992-73-1, 37267-05-3, 66419-50-9, 9002-72-6; (liothyronine) 6138-47-2, 6893-02-3; (estradiol valerate) **979-32-8**

CHEMICAL NAME: Progynova

L169 ANSWER 33 OF 41 EMBASE

ACCESSION NUMBER: 2003385827 EMBASE

TITLE: Sex steroid replacement during and after the induction of puberty.

AUTHOR: Peter F.

CORPORATE SOURCE: F. Peter, Buda Children's Hospital, Bolyai-u. 5-7, 1023 Budapest, Hungary. peter_f@elender.hu

SOURCE: Growth Hormone and IGF Research, (2003) Vol. 13, No. SUPPL. A, pp. S136-S142. .
Refs: 46
ISSN: 1096-6374 CODEN: GHIRF

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20031009
Last Updated on STN: 20031009

ABSTRACT: The main aim of sex steroid replacement during induction of puberty is to obtain a balance between healthy psychological and somatic development and optimal final height and peak bone mass (PBM). At present, the age at which it is considered appropriate to begin inducing puberty is younger than it was in the past. This trend aims for optimisation of prepubertal and pubertal growth through earlier onset of growth hormone (GH) therapy and administration of higher doses during puberty as necessary. Adequate initiation of puberty should ensure not only optimal final height and psychological balance, but also normal body proportions, appropriate bone formation and preservation of fertility for children with GH and gonadotropin deficiencies. .COPYRGT. 2003 Elsevier Science Ltd. All rights reserved.

gynecomastia: SI, side effect
fluid retention
human
male
female
adolescent
school child
article
priority journal
Drug Descriptors:
*sex hormone: AE, adverse drug reaction
*sex hormone: CB, drug combination
*sex hormone: CR, drug concentration
*sex hormone: DT, drug therapy
*sex hormone: EC, endogenous compound
*sex hormone: PK, pharmacokinetics
*sex hormone: PD, pharmacology
*sex hormone: PO, oral drug administration
*sex hormone: TD, transdermal drug administration
growth hormone: DO, drug dose
gonadotropin: EC, endogenous compound
estrogen: AE, adverse drug reaction
estrogen: CB, drug combination
estrogen: CR, drug concentration
estrogen: DT, drug therapy
estrogen: EC, endogenous compound
estrogen: PK, pharmacokinetics
estrogen: PD, pharmacology
estrogen: TD, transdermal drug administration
gonadorelin derivative: DT, drug therapy
ethinylestradiol: AE, adverse drug reaction
ethinylestradiol: CB, drug combination
ethinylestradiol: DT, drug therapy
ethinylestradiol: PK, pharmacokinetics
ethinylestradiol: PD, pharmacology
ethinylestradiol: TD, transdermal drug administration
estradiol: CR, drug concentration
estradiol: DT, drug therapy
estradiol: PK, pharmacokinetics
estradiol valerate: CB, drug combination
estradiol valerate: CR, drug concentration
estradiol valerate: DT, drug therapy
estradiol valerate: PK, pharmacokinetics
estradiol valerate: TD, transdermal drug administration
gestagen: CB, drug combination
gestagen: DT, drug therapy
luteinizing hormone: AE, adverse drug reaction
luteinizing hormone: CB, drug combination
luteinizing hormone: DT, drug therapy
luteinizing hormone: IM, intramuscular drug administration
follitropin: AE, adverse drug reaction
follitropin: CB, drug combination
follitropin: DT, drug therapy
follitropin: IM, intramuscular drug administration
methyltestosterone: AE, adverse drug reaction
methyltestosterone: DT, drug therapy
methyltestosterone: PO, oral drug administration
oxymetholone: AE, adverse drug reaction
oxymetholone: DT, drug therapy

oxymetholone: PO, oral drug administration
testosterone undecanoate: DT, drug therapy
testosterone undecanoate: PK, pharmacokinetics
testosterone undecanoate: PO, oral drug administration
testosterone enantate: DT, drug therapy
testosterone enantate: IM, intramuscular drug administration
testosterone: AE, adverse drug reaction
testosterone: CR, drug concentration
testosterone: DT, drug therapy
testosterone: PK, pharmacokinetics
testosterone: IM, intramuscular drug administration
testosterone: PO, oral drug administration
gonadorelin: DT, drug therapy
gonadorelin: PD, pharmacology

CAS REGISTRY NO.: (growth hormone) 36992-73-1, 37267-05-3, 66419-50-9, 9002-72-6; (gonadotropin) 63231-54-9; (ethinylestradiol) 57-63-6; (estradiol) 50-28-2; (estradiol valerate) **979-32-8**; (luteinizing hormone) 39341-83-8, 9002-67-9; (follitropin) 9002-68-0; (methyltestosterone) 58-18-4; (oxymetholone) 434-07-1; (testosterone undecanoate) 5949-44-0; (testosterone enantate) 315-37-7; (testosterone) 58-22-0; (gonadorelin) 33515-09-2, 9034-40-6

L169 ANSWER 34 OF 41 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2000038275 EMBASE
TITLE: Use of androgens and oestrogens in adolescents - A review of hormone replacement treatment.
AUTHOR: Zacharin M.
CORPORATE SOURCE: M. Zacharin, Dept. of Endocrinology and Diabetes, Royal Children's Hospital, Parkville, Vic. 3052, Australia
SOURCE: Journal of Pediatric Endocrinology and Metabolism, (2000) Vol. 13, No. 1, pp. 3-11. .
Refs: 75
ISSN: 0334-018X CODEN: JPEMFT
COUNTRY: Israel
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20000203
Last Updated on STN: 20000203
CONTROLLED TERM: Medical Descriptors:
*hormone substitution
*puberty
*hypogonadism
hypertension: SI, side effect
skin defect: SI, side effect
virilization
feminization
comorbidity
chronic disease
drug mixture
drug elimination
Turner syndrome: CN, congenital disorder
risk factor
child development

bone mass
child growth
sexual maturation
dose response
long term care
treatment indication
human
male
female
adolescent
review
Drug Descriptors:
*androgen: AE, adverse drug reaction
*androgen: CB, drug combination
*androgen: DO, drug dose
*androgen: PD, pharmacology
*androgen: IM, intramuscular drug administration
*androgen: SC, subcutaneous drug administration
*androgen: DL, intradermal drug administration
*estrogen: AE, adverse drug reaction
*estrogen: CB, drug combination
*estrogen: DO, drug dose
*estrogen: PD, pharmacology
*estrogen: PO, oral drug administration
*estrogen: DL, intradermal drug administration
growth hormone
ethinylestradiol: AE, adverse drug reaction
ethinylestradiol: DO, drug dose
ethinylestradiol: PK, pharmacokinetics
ethinylestradiol: PD, pharmacology
sex hormone binding globulin: EC, endogenous compound
conjugated estrogen: AE, adverse drug reaction
estradiol valerate
piperazine estrone sulfate
gestagen: CB, drug combination
medroxyprogesterone acetate: CB, drug combination
norethisterone acetate: CB, drug combination
testosterone undecanoate: DO, drug dose
testosterone undecanoate: PD, pharmacology
testosterone enantate: DO, drug dose
testosterone enantate: PD, pharmacology
chorionic gonadotropin: CB, drug combination
chorionic gonadotropin: PD, pharmacology
gonadorelin: CB, drug combination
gonadorelin: PD, pharmacology
CAS REGISTRY NO.: (growth hormone) 36992-73-1, 37267-05-3, 66419-50-9, 9002-72-6; (ethinylestradiol) 57-63-6; (estradiol valerate) **979-32-8**; (piperazine estrone sulfate) 7280-37-7; (medroxyprogesterone acetate) 71-58-9; (norethisterone acetate) 51-98-9; (testosterone undecanoate) 5949-44-0; (testosterone enantate) 315-37-7; (chorionic gonadotropin) 9002-61-3; (gonadorelin) 33515-09-2, 9034-40-6

L169 ANSWER 35 OF 41 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 93078418 EMBASE
DOCUMENT NUMBER: 1993078418
TITLE: Sex hormones and headache.
AUTHOR: Silberstein S.D.; Merriam G.R.
CORPORATE SOURCE: One Penn Boulevard,Philadelphia, PA 19144, United States

SOURCE: Journal of Pain and Symptom Management, (1993) Vol. 8, No. 2, pp. 98-114. .
ISSN: 0885-3924 CODEN: JPSMEU
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
010 Obstetrics and Gynecology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 930418
Last Updated on STN: 930418

ABSTRACT: A variety of evidence suggests a link between migraine and the female sex hormones. Women with migraine outnumber men by at least a 2:1 ratio and definite patterns of development and attacks are noted at menarche and throughout the period of menses, related to trimester of pregnancy, and again at menopause, although it may also regress. Hormonal replacement with estrogens can exacerbate migraine; oral contraceptives can change the character and frequency of migraine headache. This article will cover approaches to the therapy of hormone-related headaches associated with the menstrual cycle, menopause, and oral contraceptives.

CONTROLLED TERM: Medical Descriptors:
*estrogen therapy
*headache: DT, drug therapy
*headache: ET, etiology
***headache: SI, side effect**
*hormone action
*menstrual cycle
*oral contraception
cluster headache: ET, etiology
cluster headache: DT, drug therapy
conference paper
hormone substitution
human
intravaginal drug administration
menarche
menopause
migraine: DT, drug therapy
migraine: PC, prevention
migraine: ET, etiology
neuroendocrine system
nonhuman
oral drug administration
ovary function
pregnancy
prophylaxis
steroidogenesis
transdermal drug administration
Drug Descriptors:
*conjugated estrogen: PD, pharmacology
*conjugated estrogen: DT, drug therapy
*ergotamine: DT, drug therapy
*estrogen derivative: PD, pharmacology
*estrogen derivative: DT, drug therapy
*nonsteroid antiinflammatory agent: PD, pharmacology
*nonsteroid antiinflammatory agent: DT, drug therapy
*oral contraceptive agent: PD, pharmacology

*oral contraceptive agent: AE, adverse drug reaction
*sex hormone
antidepressant agent: DT, drug therapy
beta adrenergic receptor blocking agent: DT, drug therapy
bromocriptine mesilate: DT, drug therapy
calcium channel blocking agent: DT, drug therapy
corticosteroid: DT, drug therapy
danazol: DT, drug therapy
estradiol valerate: DT, drug therapy
ethinylestradiol: DT, drug therapy
follitropin
gonadorelin
luteinizing hormone
methysergide: DT, drug therapy
opiate peptide: PD, pharmacology
piperazine estrone sulfate: DT, drug therapy
progesterone
prolactin
prostaglandin: PD, pharmacology
quinestrol: DT, drug therapy
tamoxifen citrate: DT, drug therapy

CAS REGISTRY NO.: (ergotamine) 113-15-5, 52949-35-6; (bromocriptine mesilate) 22260-51-1; (danazol) 17230-88-5; (estradiol valerate) **979-32-8**; (ethinylestradiol) 57-63-6; (follitropin) 9002-68-0; (gonadorelin) 33515-09-2, 9034-40-6; (luteinizing hormone) 39341-83-8, 9002-67-9; (methysergide) 16509-15-2, 361-37-5, 62288-72-6; (piperazine estrone sulfate) 7280-37-7; (progesterone) 57-83-0; (prolactin) 12585-34-1, 50647-00-2, 9002-62-4; (quinestrol) 152-43-2; (tamoxifen citrate) 54965-24-1

CHEMICAL NAME: Danocrine; Nolvadex; Parlodel; Premarin; Ogen; Estraval; Estinyl; Estrovis

L169 ANSWER 36 OF 41 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:34866 TOXCENTER
COPYRIGHT: Copyright 2006 ACS
DOCUMENT NUMBER: CA14410177480Z
TITLE: Pharmaceutical-encapsulated nanoparticles for transmucosal absorption
AUTHOR(S): Mizushima, Hiroshi; Ueno, Yukio; Udagawa, Masae; Kameyama, Mieko; Suzuki, Yoshiki; Sekine, Junzo
CORPORATE SOURCE: ASSIGNEE: Ltt Biopharma Co., Ltd.
PATENT INFORMATION: JP 200628031 A2 2 Feb 2006
SOURCE: (2006) Jpn. Kokai Tokkyo Koho, 19 pp.
CODEN: JKXXAF.
COUNTRY: JAPAN
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2006:99929
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 20060207
Last Updated on STN: 20060228

ABSTRACT:
Title nanoparticles contain divalent metal salts, hydrophobic substances, and/or sugars, and pharmaceuticals encapsulated in cores having CO2H on the surface. Thus, rhodamine-encapsulated, carboxylated polystyrene nanoparticles were treated with CaCl2 to give secondary nanoparticles with particle size 50 nm, which were almost completely absorbed from jejunum in mice.
CLASSIFICATION CODE: 63-6
SUPPLEMENTARY TERMS: Miscellaneous Descriptors

carboxylated polystyrene nanoparticle transmucosal drug bioavailability; calcium chloride nanoparticle transmucosal drug bioavailability; divalent metal salt hydrophobic substance sugar nanoparticle drug bioavailability

REGISTRY NUMBER:
9004-10-8 (Insulin)
50-21-5 (Lactic acid)
50-28-2 (Estradiol)
50-50-0 (Estradiol benzoate)
50-53-3 (Chlorpromazine)
52-21-1 (Prednisolone acetate)
57-85-2 (Testosterone propionate)
58-22-0 (Testosterone)
59-05-2 (Methotrexate)
68-26-8 (Retinol)
69-93-2 (Uric acid)
143-19-1 (Sodium oleate)
144-62-7 (Oxalic acid)
302-79-4 (Retinoic acid)
315-37-7 (Testosterone enanthate)
363-24-6 (Dinoprostone)
378-44-9 (Betamethasone)
389-08-2 (Nalidixic acid)
439-14-5 (Diazepam)
497-19-8 (Sodium carbonate)
544-63-8 (Myristic acid)
745-65-3 (Alprostadil)
979-32-8 (Estradiol valerate)
1177-87-3 (Dexamethasone acetate)
1406-16-2 (Vitamin D)
1406-18-4 (Vitamin E)
2152-44-5 (Betamethasone valerate)
5104-49-4 (Flurbiprofen)
5536-17-4 (Vidarabine)
5593-20-4 (Betamethasone dipropionate)
7439-95-4Q (Magnesium, salts)
7440-50-8Q (Copper, salts)
7646-85-7 (Zinc chloride)
7705-08-0 (Ferric chloride)
9002-60-2 (ACTH)
9002-64-6 (Parathyroid hormone)
9002-72-6 (Somatotropin)
9003-53-6Q (Polystyrene, carboxylated)
9003-70-7Q (Divinylbenzene-styrene copolymer, carboxylated)
9004-96-0 (Polyethylene glycol oleate)
9007-12-9 (Calcitonin)
9010-92-8Q (Methacrylic acid-styrene copolymer, carboxylated)
9014-42-0 (Thrombopoietin)
9034-40-6 (Luteinizing hormone-releasing hormone)
9039-53-6 (Urokinase)
9054-89-1 (Superoxide dismutase)
9061-61-4 (Nerve growth factor)
10043-52-4 (Calcium chloride)
11000-17-2 (Vasopressin)
11096-26-7 (Erythropoietin)
11103-57-4 (Vitamin A)
12001-79-5 (Vitamin K)

Searched by Barb O'Bryen, STIC 2-2518

15663-27-1 (Cisplatin)
17902-23-7 (Tegafur)
21829-25-4 (Nifedipine)
22071-15-4 (Ketoprofen)
23214-92-8 (Doxorubicin)
24305-27-9 (Thyrotropin-releasing hormone)
26023-30-3 (Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)])
26100-51-6 (Lactic acid homopolymer)
33069-62-4 (Paclitaxel)
34346-01-5 (Lactic acid-glycolic acid copolymer)
54527-84-3 (Nicardipine hydrochloride)
59277-89-3 (Acyclovir)
59865-13-3 (Ciclosporin)
61422-45-5 (Carmofur)
62031-54-3 (Fibroblast growth factor)
62229-50-9 (Epidermal growth factor)
70458-96-7 (Norfloxacin)
78110-38-0 (Aztreonam)
81103-11-9 (Clarithromycin)
82419-36-1 (Ofloxacin)
83869-56-1 (Granulocyte macrophage colony-stimulating factor)
91503-79-6 (Flurbiprofen axetil)
91832-40-5 (Cefdinir)
100286-90-6 (Irinotecan hydrochloride)
104987-11-3 (Tacrolimus)
130939-66-1 (Neurotrophin 3)
139639-23-9 (Tissue plasminogen activator)
143011-72-7 (Granulocyte colony-stimulating factor)
145040-37-5 (Candesartan cilexetil)
154598-52-4 (Efavirenz)
169494-85-3 (Leptin)
170277-31-3 (Infliximab)
185243-69-0 (Etanercept)

REGISTRY NUMBER: 111470-99-6

L169 ANSWER 37 OF 41 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:187800 TOXCENTER
COPYRIGHT: Copyright 2006 ACS
DOCUMENT NUMBER: CA12124286617V
TITLE: Permeation enhancement of topical pharmaceuticals by inducing phase separation of epithelial lipid bilayers
AUTHOR(S): Elias, Peter M.; Thornfeldt, Carl R.; Feingold, Kenneth R.; Holleran, Walter M.
CORPORATE SOURCE: ASSIGNEE: Regents of the University of California
PATENT INFORMATION: WO 9421271 A1 29 Sep 1994
SOURCE: (1994) PCT Int. Appl., 29 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1994:686617
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020917

ABSTRACT:
Topical compns. containing ≥1 intercellular phase-separating agent, such as epicholesterol (I), are used for inducing phase separation of the epithelial multilayered lipid bilayers within the intercellular spaces of the stratum corneum in a host in need of the topical administration of a physiol. active

substance. Combination of I with transvaccenic acid in propylene glycol/EtOH delivered LHRH at 4.7 times the amount delivered by the vehicle. A lotion contained estradiol valerate 1-10, cetyl alc. 200, propylene glycol 100, Na lauryl sulfate 15, I 10 g, and water 400mL.
CLASSIFICATION CODE: 63-6
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
permeation phase sepn epithelial lipid bilayer; topical permeation enhancer epithelial lipid bilayer; transvaccenic acid epicholesterol etradiol lotion
REGISTRY NUMBER: 53-86-1 (Indomethacin)
54-05-7 (Chloroquine)
57-55-6 (Propylene glycol)
57-88-5 (Cholesterol)
58-08-2 (Caffein)
67-68-5 (Dmso)
76-41-5 (Oxymorphone)
77-86-1 (Tris)
79-63-0 (Lanosterol)
111-02-4 (Squalene)
124-30-1 (Stearylamine)
128-33-6 (Zymosterol)
128-53-0 (n-Ethylmaleimide)
137-58-6 (Lidocaine)
143-28-2 (Oleyl alcohol)
303-43-5 (Cholesterol oleate)
313-04-2 (Desmosterol)
404-86-4 (Capsaicin)
434-16-2 (7-Dehydrocholesterol)
474-77-1 (Epicholesterol)
601-34-3 (Cholesterol palmitate)
693-72-1 (Trans-Vaccenic acid)
979-32-8 (Estradiol valerate)
1256-86-6 (Cholesterol sulfate)
1393-88-0 (Gramicidin d)
1908-11-8 (Cholesterol laurate)
1989-52-2 (Cholesterol myristate)
2001-95-8 (Valinomycin)
2387-23-7 (Dicyclohexylcarbodiamide)
2573-03-7 (Cholesterol arachidate)
7365-45-9 (Hepes)
9034-40-6 (Lhrh)
11000-17-2 (Vasopressin)
11054-70-9 (Lasalocid)
17090-79-8 (Monesin)
20350-15-6 (Brefeldin a)
28380-24-7 (Nigericin)
33507-63-0 (Substance p)
35602-69-8 (Cholesterol stearate)
51013-18-4 (Methyl pyrrolidone)
53003-10-4 (Salinomycin)
59227-89-3 (1-Dodecylazacycloheptan-2-one)
60299-11-8 (Nifedipine hydrochloride)
88899-55-2 (Bafilomycin a1)
88899-56-3 (Bafilomycin b1)

L169 ANSWER 38 OF 41 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:567563 TOXCENTER
DOCUMENT NUMBER: DART-TER-93001533
TITLE: Hormones and hormonal antagonists.
AUTHOR(S): Schardein J L

CORPORATE SOURCE: International Research and Development Corporation, Mattawan, MI.
SOURCE: Chemically Induced Birth Defects, (1993) 2 271-339. Ref: 687.
ISBN: 0-8247-8775-7.
DOCUMENT TYPE: (CHAPTER)
(REVIEW, ACADEMIC)
General Review; (REVIEW)
FILE SEGMENT: DART
LANGUAGE: English
ENTRY DATE: Entered STN: 20040203
Last Updated on STN: 20040203
CONTROLLED TERM: Check Tags: Animal; Human; Female
Pregnancy
*Abnormalities, Drug-Induced
Androgens: TO, TOXICITY
Estrogens: TO, TOXICITY
Progestational Hormones: TO, TOXICITY
*Androgen Antagonists: TO, TOXICITY
*Estrogen Antagonists: TO, TOXICITY
*Adrenal Cortex Hormones: TO, TOXICITY
*Sex Hormones: TO, TOXICITY
REGISTRY NUMBER: 2363-58-8 (2-alpha,3-alpha-Epithio-5-alpha-androstan-17-beta-ol)
2529-46-6 (17-alpha-(2-Methallyl)-19-nortestosterone)
434-22-0 (Nandrolone)
5630-53-5 (Tibolone)
17924-92-4 (Zearalenone)
57-85-2 (Testosterone)
521-10-8 (Methandriol)
58-18-4 (Methyltestosterone)
17230-88-5 (Danazol)
57-83-0 (Progesterone)
56-53-1 (Diethylstilbestrol)
50-50-0 (Estradiol benzoate)
113-38-2 (Estradiol dipropionate)
979-32-8 (Estradiol valerate)
57-63-6 (Ethinyl estradiol)
53-16-7 (Estrone)
50-27-1 (Estriol)
1169-79-5 (Quinestradiol)
2624-43-3 (Cyclofenil)
84-17-3 (Dienestrol)
53-03-2 (Prednisone)
124-94-7 (Triamcinolone)
84-16-2 (Hexestrol)
302-22-7 (Chlormadinone acetate)
297-76-7 (Ethynodiol diacetate)
52-76-6 (Lynestrenol)
71-58-9 (Medroxyprogesterone acetate)
68-22-4 (Norethindrone)
68-23-5 (Norethynodrel)
1477-57-2 (Fertilysin)
926-93-2 (Methallibure)
434-03-7 (Ethisterone)
152-62-5 (Dydrogesterone)
432-60-0 (Allylestrenol)
38673-38-0 (Norethindrone acetate)
68-96-2 (Hydroxyprogesterone)
520-85-4 (Medroxyprogesterone)

79-64-1 (Dimethisterone)
302-23-8 (Hydroxyprogesterone acetate)
630-56-8 (Hydroxyprogesterone caproate)
797-63-7 (Norgestrel)
2098-66-0 (Cyproterone)
911-45-5 (Clomiphene)
67-98-1 (Ethamoxytriphetol)
10448-84-7 (Nitromifene)
9002-60-2 (Corticotropin)
9002-61-3 (Human chorionic gonadotropin)
9002-70-4 (Pregnant mare's serum gonadotropin)
9002-71-5 (Thyrotropin)
11000-17-2 (Vasopressin)
61489-71-2 (Human menopausal gonadotropin)
378-44-9 (Betamethasone)
4419-39-0 (Beclomethasone)
50-22-6 (Corticosterone)
51333-22-3 (Budesonide)
54063-32-0 (Clobetasone)
53-06-5 (Cortisone)
382-67-2 (Desoxymetasone)
64-85-7 (Desoxycorticosterone)
50-02-2 (Dexamethasone)
2607-06-9 (Diflucortolone)
152-97-6 (Fluocortolone)
3385-03-3 (Flunisolide)
50-23-7 (Hydrocortisone)
6000-74-4 (Hydrocortisone sodium phosphate)
2668-66-8 (Medrysone)
83-43-2 (Methylprednisolone)
50-24-8 (Prednisolone)
72-33-3 (Mestranol)
11085-36-2 (Human placental lactogen)
9034-40-6 (Gonadotropin-releasing hormone)
125-04-2 (Hydrocortisone sodium succinate)
13609-67-1 (Hydrocortisone 17-alpha-butyrate)
897-06-3 (delta-1,4-Androstadiene-3,17-dione)
1852-53-5 (Androstanediol, 3alpha,17beta-)
846-46-8 (Androstanedione)
633-35-2 (1,4,6-Androstatriene-3,17-dione)
521-17-5 (Androstenediol)
63-05-8 (Androstenedione)
53-41-8 (Androsterone)
17021-26-0 (Calusterone)
248-66-2 (2alpha-Cyano-4,4,17alpha-trimethylandrost-5-en-17beta-ol-3-one)
53-43-0 (Dehydroepiandrosterone)
521-18-6 (Dihydrotestosterone)
965-90-2 (Ethylestrenol)
20799-24-0 (17alpha-Ethynyl-17beta-acetoxy-19-norandrost-4-en-3-one oxime)
98319-26-7 (Finasteride)
76-43-7 (Fluoxymesterone)
1424-00-6 (Mesterolone)
3704-09-4 (Mibolerone)
797-58-0 (Norbolethone)
52-78-8 (Norethandrolone)
434-07-1 (Oxymetholone)
10418-03-8 (Stanozolol)
26538-44-3 (Zeranol)

57-91-0 (Estradiol, alpha-)
50-28-2 (Estradiol, 17beta-)
7642-52-6 (17-Ethinyl-7alpha-methyl-19-nortestosterone)
21327-74-2 (F 6103)
152-43-2 (Quinestrol)
43085-16-1 (STS 153)
65928-58-7 (STS 557)
24356-94-3 (Algestone acetophenide)
1961-77-9 (Chlormadinone)
427-51-0 (6-Chloro-delta6-1,2alpha-methylene-17alpha-hydroxyprogesterone acetate)
2529-45-5 (Flurogestone acetate)
145-15-3 (20beta-Hydroxy-pregn-4-en-3-one)
595-33-5 (Megestrol acetate)
2919-66-6 (Melengestrol acetate)
128-20-1 (Pregnanolone)
2755-10-4 (Retroprogesterone)
8056-92-6 (Ethynodiol diacetate-mestranol)
8015-14-3 (Lynestrenol-mestranol)
8015-29-0 (Norethindrone-mestranol)
8015-30-3 (Norethynodrel-mestranol)
8056-51-7 (Norgestrel-ethinyl estradiol)
79-01-6 (TRI)
31477-60-8 (Centchroman)
34616-48-3 (5-((2-Chlorobenzylidine)-amino)-isoquinoline)
38641-70-2 (N-(2-Chloro-1-naphthylidene)-3-amino-2:6-lutidene)
64959-26-8 (N-(2-Chloro-1-naphthylidene)aniline)
40226-25-3 (N-(2-Chloro-1-naphthylidene)-o-anisidine)
40226-23-1 (N-(2-Chloro-1-naphthylidene)-o-toluidine)
40226-24-2 (N-(2-Chloro-1-naphthylidene)-p-toluidine)
38641-71-3 (N-(2-Chloro-1-naphthyl)-N-phenylmethylamine)
33204-76-1 (2,6-cis-Diphenylhexamethyl-cyclotetrasiloxane)
467-77-6 (Coronaridine)
71743-82-3 (1,2-Diethyl-1,3-bis-p-hydroxyphenyl-1-propene)
1945-67-1 (Dimethylglyoxal-bis-(guanylhydrazone))
1945-68-2 (Ethylglyoxal-bis-guanylhydrazone)
595-57-3 (9alpha-Fluoro-11beta,17-dihydroxy-3-oxo-4-androstene-17alpha-propionic acid)
76430-81-4 (Glyoxal-bis(guanylhydrazone) diacetate)
109-56-8 (2-Isopropylamino ethanol)
1945-62-6 (Malonaldehyde-bis-guanylhydrazone)
21658-26-4 (p-Nitrophenyl-p'-guanidino benzoate)
7698-97-7 (ORF-3858)
16550-39-3 (ORF-4563)
27953-80-6 (ORF-5656)
76584-58-2 (2-Oxophenylacetaldehyde-1-guanylhydrazone)
53305-31-0 (DL-6-(N-alpha-Pipecolinomethyl)-5-hydroxyindane maleate)
6237-78-1 (Pyruvic acid guanylhydrazone)
76567-36-7 (Quinone oxime guanylhydrazone)
1238-54-6 (SCH 10015)
20835-91-0 (5-alpha-Stigmastane-3beta-5,6beta-triol-3-monobenzoate)
13073-86-4 (SU-13320)
3646-61-5 (U-10293)
3414-47-9 (U-11634)
24543-59-7 (6alpha-Bromo-17beta-methyl-4-oxa-5alpha-androstan-3-one)
39962-28-2 (N-3,5-Dimethyl-4-isoxazolyl-methyl

phthalimide)
13311-84-7 (Flutamide)
65121-68-8 (1-(p-(2-N,N-Diethylaminoethoxy)phenyl)-1,2-di-(p-methoxyphenyl)-but-1-ene)
21708-94-1 (1-[p-(beta-Diethylaminoethoxy)phenyl]-2-nitro-1,2-diphenyl ethylene)
6732-77-0 (1[p-(beta-Diethylaminoethoxy)phenyl]-1-phenyl-2-(p-methoxyphenyl)-ethane)
37820-57-8 (1-[p-(beta-Dimethylaminoethoxy)phenyl]-2-nitro-1,2-diphenyl ethylene)
1845-11-0 (Nafoxidine)
10540-29-1 (Tamoxifen)
89778-26-7 (Toremifene)
9002-72-6 (Anterior pituitary hormone)
33515-09-2 (Gonadorelin)
9034-42-8 (beta-Melanotropin)
9002-64-6 (Parathormone)
9002-62-4 (Prolactin)
24305-27-9 (Thyrotropin-releasing hormone)
66734-13-2 (Alclometasone)
52-39-1 (Aldosterone)
2135-17-3 (Flumethasone)
145-13-1 (Pregnenolone)

CHEMICAL NAME: 0 (Androgens); 0 (Estrogens); 0 (Progestational hormones); 0 (Androgen antagonists); 0 (Estrogen antagonists); 0 (Adrenal cortex hormones); 0 (Sex hormones); 0 (Oral contraceptives); 0 (Menotropins); 0 (Conjugated estrogens); 0 (16beta-Bromo-3beta,17-hydroxy-5alpha-pregnane-11,20-dione); 0 (Dihydroisoandrosterone); 0 (Hydroxymethylandrosterone); 0 (2,3-Diphenyl-6-methoxy-1-(N-methyl-N-propargyl) aminoindene); 0 (2,3-Diphenyl-1-(N-methyl-N-propargyl) aminoindene); 0 (Ethylene-bis-guanide copper sulfate); 0 (Phenylglyoxal-bis(guanylhydrazone)); 0 (o-Phthalaldehyde-bis-(guanylhydrazone)); 0 (Succinaldehyde-bis(guanylhydrazone)); 0 (1-(p-(2-N,N-Diethylaminoethoxy)phenyl)-1,2-di-(p-methoxyphenyl)-3-methyl-but-1-e ne); 0 (1-(p-(beta-Diethylaminoethoxy)phenyl)-1,2-diphenyl ethylene); 0 (2-[p-(6-Methoxy-2-phenyliden-3-ly)phenoxy]triethylamine); 0 (Menotropins)

L169 ANSWER 39 OF 41 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:74669 TOXCENTER
COPYRIGHT: Copyright (c) 2006 The Thomson Corporation
DOCUMENT NUMBER: PREV198579030165
TITLE: POLYCYSTIC OVARIAN CONDITION IN ESTRADIOL VALERATE-TREATED RATS SPONTANEOUS CHANGES IN CHARACTERISTIC ENDOCRINE FEATURES
AUTHOR(S): SCHULSTER A [Reprint author]; FAROOKHI R; BRAWER J R
CORPORATE SOURCE: DEP OF OBSTET AND GYNECOL, F3 WOMEN'S PAVILION, ROYAL VICTORIA HOSP, 687 PINE AVE WEST, MONTREAL, QUEBEC, H3A 1A1, CANADA
SOURCE: Biology of Reproduction, (1984) Vol. 31, No. 3, pp. 587-594.
CODEN: BIREBV. ISSN: 0006-3363.
DOCUMENT TYPE: Article
FILE SEGMENT: BIOSIS
OTHER SOURCE: BIOSIS 1985:250169
LANGUAGE: ENGLISH

ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

ABSTRACT:
A chronic anovulatory polycystic ovarian (PCO) condition can be induced in rats with estradiol valerate (EV). The early stages (8-10 wk after EV treatment) of the condition are characterized by low basal plasma luteinizing hormone (LH) and estradiol concentrations, as well as poor LH responsiveness to LHRH. Alterations in pituitary LH secretory activity may be involved in induction and maintenance of the PCO condition. To examine this possibility basal plasma LH and FSH concentrations were measured at various times (6, 15, 20 and 22 wk) after treatment with EV. At 22 wk, animals were subjected to a double LHRH pulse or equivalent treatment with saline. Basal plasma LH concentrations in EV-treated animals doubled between 6 and 22 wk. Despite this sharp increase, basal plasma LH concentrations at 22 wk were still significantly lower in EV-treated animals compared to proestrous controls. Basal FSH in EV-treated animals remained in the proestrous range throughout the 22-wk period. Pituitary FSH and LH secretions in response to the LHRH challenge were significantly greater in EV-treated animals compared to proestrous controls. Plasma estradiol was significantly greater at 22 wk post-EV treatment than at 9 wk and this difference was reflected in the histology of the endometrium. A PCO condition is compatible with radical alterations in basal LH, and responsiveness to LHRH. Aberrations in the ability to secrete LH do not appear to be causal in maintaining the condition.

CLASSIFICATION CODE: Microscopy - Histology and histochemistry 01056
Cytology - Animal 02506
Circadian rhythms and other periodic cycles 07200
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Sterols and steroids 10067
Biochemistry studies - Carbohydrates 10068
Anatomy and Histology - Microscopic and ultramicroscopic anatomy 11108
Metabolism - Carbohydrates 13004
Metabolism - Sterols and steroids 13008
Metabolism - Proteins, peptides and amino acids 13012
Blood - Blood and lymph studies 15002
Reproductive system - General and methods 16501
Reproductive system - Pathology 16506
Endocrine - Gonads and placenta 17006
Endocrine - Pituitary 17014
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Endocrine system 22016
Pharmacology - Reproductive system and implantation studies 22028
Toxicology - Pharmacology 22504
Development and Embryology - Descriptive teratology and teratogenesis 25552

SUPPLEMENTARY TERMS: Major Concepts
Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Morphology; Pharmacology; Reproductive System (Reproduction); Toxicology

SUPPLEMENTARY TERMS: Miscellaneous Descriptors
ENDOMETRIUM PITUITARY ALTERATION LUTEINIZING HORMONE LHRH FSH

ORGANISM: Classifier
Muridae 86375
Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: **979-32-8** (ESTRADIOL VALERATE)
9002-67-9 (LUTEINIZING HORMONE)
9034-40-6 (LHRH)
9002-68-0 (FSH)

L169 ANSWER 40 OF 41 TOXCENTER COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:63320 TOXCENTER
COPYRIGHT: Copyright (c) 2006 The Thomson Corporation
DOCUMENT NUMBER: PREV198069071126
TITLE: EFFECTS OF ESTRADIOL INDUCED LESIONS OF THE ARCUATE NUCLEUS ON GONADOTROPIN RELEASE IN RESPONSE TO PREOPTIC STIMULATION IN THE RAT
AUTHOR(S): BRAWER J R [Reprint author]; RUF K B; NAFTOLIN F
CORPORATE SOURCE: DEP OBSTET GYNECOL, R VICTORIA HOSP, WOMENS PAVILLON, 687 PINE AVE W, MONTREAL, QUE H3A 1A1, CAN
SOURCE: Neuroendocrinology, (1980) Vol. 30, No. 3, pp. 144-149. CODEN: NUNDAJ. ISSN: 0028-3835.
DOCUMENT TYPE: Article
FILE SEGMENT: BIOSIS
OTHER SOURCE: BIOSIS 1980:196130
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

ABSTRACT:
Female Wistar rats treated with a single s.c. injection of 2 mg estradiol valerate (EV) develop gradually progressive, multifocal lesions of the arcuate nucleus. They also exhibit persistent vaginal estrus and endocrine profiles characteristic of animals sustaining anterior hypothalamic deafferentiation. In this study, EV-treated females with the arcuate lesions released significantly less LH [lutropin] 1 h following electrochemical stimulation of the medial preoptic area (MPOA) than did normally cycling controls in proestrus. FSH [follitropin] release in response to MPOA stimulation was the same for both groups. As plasma LH concentrations were not significantly different between EV-treated and control animals 1 h after the injection of a potent LHRH [luliberin] analog, the reduced LH response to MPOA stimulation appears to reflect a primarily hypothalamic defect. However, the EV treatment also affected pituitary responsiveness to long-term stimulation as evidenced by reduced LH responses to the LHRH analog after 2 and 3 h. No such differences were seen in the FSH response.

CLASSIFICATION CODE: Circadian rhythms and other periodic cycles 07200
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Sterols and steroids 10067
Biochemistry studies - Carbohydrates 10068
External effects - Electric, magnetic and gravitational phenomena 10610
Metabolism - Carbohydrates 13004
Metabolism - Sterols and steroids 13008
Metabolism - Proteins, peptides and amino acids 13012
Reproductive system - Physiology and biochemistry 16504
Reproductive system - Pathology 16506
Endocrine - Gonads and placenta 17006
Endocrine - Pituitary 17014
Endocrine - Neuroendocrinology 17020
Integumentary system - General and methods 18501
Nervous system - General and methods 20501

Nervous system - Physiology and biochemistry 20504
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Endocrine system 22016
Routes of immunization, infection and therapy 22100
Toxicology - Pharmacology 22504

SUPPLEMENTARY TERMS: Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination); Pharmacology; Reproductive System (Reproduction)

SUPPLEMENTARY TERMS: Miscellaneous Descriptors
LULIBERIN HORMONE-DRUG ESTRADIOL VALERATE LUTROPIN FOLLITROPIN

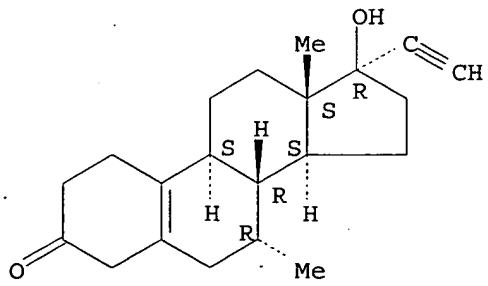
ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 50-28-2 (ESTRADIOL)
9034-40-6 (LULIBERIN)
979-32-8 (ESTRADIOL VALERATE)
152923-57-4 (LUTROPIN)
9002-68-0 (FOLLITROPIN)
9002-67-9 (LUTROPIN)

L169 ANSWER 41 OF 41 ADISINSIGHT COPYRIGHT (C) 2006 Adis Data Information BV on STN

ACCESSION NUMBER: 1998:7442 ADISINSIGHT
SOURCE: Adis R&D Insight
DOCUMENT NO: 008188
CHANGE DATE: Feb 16, 2006
GENERIC NAME: Tibolone
SYNONYM: KB 889; ORG OD 14; ORG OD14
CHEMICAL NAME: 19-Norpregn-5(10)-en-20-yn-3-one, 17-hydroxy-7-methyl-, (7alpha, 17alpha)-
TRADE NAME: Boltin(R); Livial(R); Liviella(R); Livifem(R); Paraclim(R); Xyvion(TM)
MOLECULAR FORMULA: C21 H28 O2
CAS REGISTRY NO.: 5630-53-5
STRUCTURE:

Absolute stereochemistry.



EPHMRA ATC CODE: G3 Sex Hormones and Products with Similar Desired Effects, Systemic Action Only; G3B Androgens, Excluding G3E, G3F; G3H Other Sex Hormones and Similar Products; L2A Cytostatic Hormones; M5X All Other Musculoskeletal Products
WHO ATC CODE: G03 Sex Hormones and Modulators of the Genital System; G03C-B Synthetic estrogens, plain; G03X Other Sex Hormones and Modulators of the Genital System; G03X-C Selective estrogen receptor modulators; L02A Hormones and Related Agents; M05B-X Other drugs affecting bone structure and mineralization
HIGHEST DEV. PHASE: Launched

CURRENT DEVELOPMENT STATUS:
Launched, Asia, Menopausal syndrome
Launched, Australia, Menopausal syndrome
Launched, Europe, Menopausal syndrome
Launched, France, Menopausal syndrome
Launched, Latin America, Menopausal syndrome
Launched, Norway, Menopausal syndrome
Launched, World, Menopausal syndrome
Launched, Argentina, Postmenopausal osteoporosis prevention
Launched, Asia, Postmenopausal osteoporosis prevention
Launched, Europe, Postmenopausal osteoporosis prevention
Launched, Latin America, Postmenopausal osteoporosis prevention
Launched, Scandinavia, Postmenopausal osteoporosis prevention
Registered, United States, Postmenopausal osteoporosis prevention
Preregistration, Canada, Menopausal syndrome
Preregistration, United States, Menopausal syndrome
Preregistration, Canada, Postmenopausal osteoporosis prevention
Preregistration, Japan, Postmenopausal osteoporosis treatment
Phase III, Europe, Breast cancer
Phase III, Japan, Menopausal syndrome
Clinical (Phase Unknown), Australia, Female sexual dysfunction
Clinical (Phase Unknown), Europe, Female sexual dysfunction
Clinical (Phase Unknown), United States, Female sexual dysfunction

COMPANY INFORMATION
ORIGINATOR: Nourypharma (Germany)
PARENT: Akzo Nobel
LICENSEE: Elea; Nippon Organon; Organon

OTHER SOURCES: 809022484; 809037749; 809033241; 800708242; 800742374; 800855632; 800714153; 800933006; 800540966; 800521913; 800551086; 807120199; 800748139; 800672800; 800720849; 800465194; 807201067; 800494778; 800916727; 800443030; 800691857; 800698900; 800673840; 807172782; 800779944; 807200205; 800738134; 800818370; 800833752; 800809422; 800810917; 800671375; 800924592; 807162624; 800833829; 800917174; 800797271; 800494741
WORD COUNT: 5323

TEXT
Introduction:
Tibolone (ORG OD 14, ORG OD14, KB 889, Livial sup((R)), Liviella sup((R)), Livifem sup((R)), Boltin sup((R)), Xyvion(TM), Paraclim sup((R))) is a synthetic steroid belonging to a class of menopausal drugs known as selective tissue estrogenic activity regulator (STEAR), which does not contain estrogen or progestogen. It has estrogenic, progestogenic as well as androgenic properties. Tibolone is indicated for menopausal symptoms associated with

hormone deficiency and osteoporosis. Its action is mainly facilitated by the tissue-specific effects of its three metabolites, which activates specific receptors; the 3alpha-OH and 3beta-OH metabolites display their activity via the estrogen receptor, while the Delta4 metabolite has affinity for the androgen and progesterone receptors/1/.

Tibolone is a tissue-selective estrogen agonist, acting as an estrogen in some tissues including the brain, bone, vaginal tissue and blood vessels, but not acting as an estrogen on the endometrium or breast tissue. In addition, tibolone is mildly androgenic and increases free testosterone among women. Since several motivational aspects of sexual functioning are androgen-dependent, this steroid could also be beneficial in the management of sexual dysfunction in postmenopausal women. The product is available as a 2.5mg daily dose in more than 80 countries worldwide for a variety of indications.

Company agreements

Tibolone is in development with Organon and Nourypharma (both subsidiaries of Akzo Nobel) and is licensed to Nippon Organon in Japan. Donmed, the South African agent of Organon, markets Livifem sup((R)) in South Africa.

Key development milestones

Osteoporosis and menopausal disorders: tibolone has been launched as a hormonal replacement therapy (HRT) for the treatment of menopausal disorders and for the prevention of postmenopausal osteoporosis in more than 70 countries worldwide, including most Asian, European and Latin American countries, but excluding the US, Canada and Japan. The product is marketed as Livifem sup((R)) in South Africa, Boltin sup((R)) in Spain, Paraclim in Argentina (by ELEA pharmaceuticals) and Livial sup((R)) in other countries.

Studies in the US were conducted at different dosages (1.25 and 0.625mg) from those in other markets (2.5mg) and an application for approval as therapy for the prevention of postmenopausal osteoporosis and as HRT has been made with the FDA. Subsequently, following a request for further information, the FDA has approved tibolone for use in postmenopausal osteoporosis. However, the product will not be launched in the US because labelling is still under FDA review. Additional studies are ongoing in US to address the FDA's labelling concerns. Tibolone is forecasted for launch in the US by the end of 2006, following completion of additional phase III trials in 2005.

Tibolone is also awaiting approval in Canada for the treatment of menopausal disorders and for the prevention of postmenopausal osteoporosis. It is undergoing phase III trials for menopausal syndrome and is awaiting approval for treatment of postmenopausal osteoporosis in Japan; regulatory authorities there have delayed approval of the drug.

In February 2006, Organon announced its decision to close the LIFT ("Long term Intervention on Fractures and other endpoints Trial") study earlier than scheduled, based on the recommendation from the independent study Data & Safety Monitoring Board (DSMB) and Steering Committee. According to interim results, tibolone did decrease the incidence of vertebral fractures, but this was also associated with more strokes versus controls; further DSMB's analysis in January 2006 revealed that such findings had persisted. Consequently, trial investigators and patients have been informed and treatment halted to conduct final assessments. Following full data analysis, Organon will reconsider clinical activities of tibolone for this indication/2/. LIFT was a global, 5-year, randomised, double-blind study investigating tibolone 1.25mg among elderly patients at high risk of osteoporotic fractures. The trial was initiated in July 2001 and completed enrolment in June 2003 with 4538 subjects at > 50 sites located worldwide, including Argentina, Australia, Belgium, Brazil, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Mexico, the

Netherlands, Norway, Poland, Slovakia, Spain, the UK, Venezuela and the US/3/.

Breast cancer: tibolone is in clinical development for the treatment of breast cancer. The LIBERATE (Livial sup((R)) Intervention following Breast cancer Efficacy, Recurrence And Tolerability Endpoints) trial is ongoing among women with a history of breast cancer afflicted by the climacteric symptoms of menopause; patients will be followed for 5 years. Recruitment for the LIBERATE trial started in 2002 and aims to enrol 2600 women in 26 countries, including the Netherlands; other countries have not been specified. In July 2004, Organon announced that > 2200 women have been enrolled in the study involving 260 clinical centres; preliminary data are anticipated in July 2006/4/. LIBERATE trial completion is forecasted in 2008.

In vitro studies have shown that tibolone induces apoptosis in breast cancer cells. Tibolone has also demonstrated anti-ischaemic properties similar to estrogen and may have potential in the prevention of primary and secondary coronary artery disease.

Female sexual dysfunction: Organon is sponsoring a major international study, called LISA (Livial International Study in sexual Arousal disorders) to investigate tibolone 2.5mg for the management of sexual dysfunction among healthy postmenopausal women with an intact uterus. This 6-month, double-blind, double-dummy, randomised trial has been designed to compare tibolone with transdermal estrogen and progestogen therapy. The primary objective of LISA is to evaluate the effects of tibolone on sexual functioning over and above its established ability to relieve climacteric symptoms among this patient population. Only subjects with sexual dysfunction caused by personal distress and not considered to be caused by relationship/partner problems will be eligible to participate/5/. A total of 360 women being recruited at = 25 clinical centres in Europe, the US and Australia; trial enrolment commenced in March 2004 with availability of initial results anticipated by the end of 2005.

Tibolone potentially provides postmenopausal women experiencing sexual dysfunction and impaired well-being with an effective treatment option. It has been shown to improve the mental and sexual well-being of postmenopausal via the drug's effects in influencing libido, arousal and satisfaction. In addition, randomised studies indicate that tibolone improves libido and sexual responsiveness to a greater extent than the conventional estrogen-progestogen therapies/6/.

Product manufaturing: in November 2003, Organon Pharmaceutical announced the official opening of its extended and upgraded factory in Nanjing, China. The factory is fully upgraded for the GMP (Good Manufacturing Practice) production and packaging of pharmaceutical tablets for the local market, which includes Livial sup((R)). This investment confirms the growing importance of the pharmaceutical market in China for Organon.

EVALUATION:
Menopausal syndrome 74 (PO).
Postmenopausal osteoporosis prevention 74 (PO).
Postmenopausal osteoporosis treatment 74 (PO).

COMMERCIAL SUMMARY:
Osteoporosis + menopause / Steroid

Company	Region	Launch Date	Peak Sales	Patent Expiry
Akzo Nobel	Eur	Feb-1997	$200m	2010
Akzo Nobel	Japan	2008	$50m	2010
Akzo Nobel	US	2007	$300m	

PHARMACOLOGY OVERVIEW:
Pharmacodynamics:
Significant inhibitory effect in human breast cancer cells; inhibits local production of estradiol in breast tissue; increases loss of trabecular but not cortical bone density
Mechanism of action:
Androgen agonists
Progesterone agonists
Selective tissue estrogenic activity regulators

CLINICAL OVERVIEW:
Route(s) of Administration: PO
Administration Freq.(per day):
Adverse events:
most frequent: Vaginal bleeding.
occasional: Breast pain, Dizziness, Headache, Migraine, Nausea, Skin disorders, Weight gain.
rare: Hirsutism, Nervousness, Oedema.
Drug Interactions:
Moderate. Tibolone may interact with liver enzyme-inducing drugs and with anticoagulants

Adverse Events:
The adverse reaction profile of tibolone is similar to other hormone replacement therapies. The adverse reactions of tibolone reported most commonly to the UK Committee on Safety of Medicines and Medicines Control Agency include headache, dizziness, nausea, rash, pruritus and weight gain. Other adverse effects of tibolone are vaginal bleeding, migraine and visual disturbances. Vaginal bleeding can occur in 8-9% of tibolone recipients/7/.

A UK study found that younger women, women who are recently menopausal and those who have detectable estradiol levels are more likely to report vaginal bleeding while taking tibolone. They also report that even if women do bleed, there is no evidence of endometrial stimulation, or hyperplasia. The researchers compared the incidence of vaginal bleeding in 59 recently menopausal women who received tibolone 2.5mg daily (treatment group), with 53 similar women who received no medication (control group). In the treatment group, 12 women (20%) reported vaginal bleeding. In those who bled, the age of menopause, and the months since last menstrual period were significantly lower, compared to those who did not bleed. In true postmenopausal (12 months after the last menstrual period) the incidence of bleeding was 12%. The number of women who bled in the treatment group who had detectable estradiol levels > 70 pmol/L, was significantly higher, compared to the control group. Only 17% of those who bled in the treatment group had any bleeding after the first 3 months of tibolone treatment. In the control group 75 women (9.4%) reported bleeding. Those who bled in this group were closer to their last menstrual period than those who did not bleed, and the number who had detectable estradiol levels was significantly higher in those who bled than in those who did not. In truly menopausal women the incidence of bleeding was 2.3%/8/.

In a 48-week study in 423 women with menopausal symptoms, vaginal bleeding occurred significantly less often with tibolone than with estradiol/norethisterone. In addition, amenorrhoea was achieved more quickly with tibolone than with estradiol/norethisterone. There were also significantly fewer reports of breast tenderness with tibolone therapy compared with estradiol/norethisterone/9/. However, a study in 235 patients randomised to treatment with tibolone or **estradiol valerate** /norethisterone for 12 months found the incidence of the main adverse events of bleeding, breast tenderness and headache to be comparable between the 2

treatment groups/10/.
Tibolone (2.5 mg/day) and estradiol (50 microg/day) had comparable tolerability in a trial in 76 women with surgical menopause. No adverse events were reported in 23/32 (72%) of patients in the tibolone group and 24/34 (71%) in the estradiol group. Adverse events associated with tibolone included nausea (12%) and weight gain, oedema, facial hair, endometriosis and nervousness (1 patient each). Events reported in the estradiol group were nausea (3%), skin irritation from pathces (12%), breast tenderness (9%), weight gain (6%), oedema (3%) and headache (3%)/11/.
88 women with symptomatic osteoporosis were randomised to receive oral tibolone 2.5 mg/day (n = 45), or placebo (43), for 2 years. All patients also received calcium 800 mg/day. 14/88 (15.9%) women discontinued therapy because of adverse events including breast tenderness, increased bodyweight and nausea. 60% of tibolone recipients and 54% of placebo recipients experienced >= 1 adverse event, while vaginal bleeding or spotting was reported by 31 and 12.2% of patients in the respective treatment groups/12/.
In April 2002, Organon reported that tibolone is significantly better tolerated than conventional hormone replacement therapy (continuous combined estradiol plus northindrone acetate), according to results from the first study (n = 225) to compare these therapies' tolerability and efficacy on postmenopausal bone loss. The study showed that while both therapies are equally effective, tibolone is markedly less likely to cause vaginal bleeding and breast pain, and therefore provides postmenopausal women with a more acceptable first-line therapy for the protection of bone health/13/.
The most common events in women receiving tibolone or no treatment for the prevention of postmenopausal osteoporosis for 10 years were menopausal vaginal bleeding (34 vs 14%), hypertension (15 vs 22%) and weight increase (15 vs 0%)/14/.
Drug Interactions:
Phenytoin, carbamazepine, rifampicin and other drugs which induce liver enzymes can reduce the effectiveness of tibolone by accelerating its metabolism. Tibolone may increase the effect of anticoagulants.

PHARMACOLOGY:
Pharmacokinetics:
Tibolone is rapidly and almost completely absorbed after oral administration. Peak plasma levels are reached after 1.5-4h and are 2.3-7.8% of the dose administered/litre. Cumulative excretion in the urine is = 30% of the tibolone dose/15/.
There are 3 primary metabolites of tibolone: the delta sup(4)-isomer, the 3alpha-hydroxy metabolite and the 3beta-hydroxy metabolite. All 3 of these metabolites and tibolone itself are pharmacologically active. The main binding affinities of tibolone and the delta sup(4)-isomer are progestogenic and androgenic, whereas the main affinity for the hydroxy metabolites is estrogenic/15/.
96.3% of tibolone is bound to protein in human female serum in vitro. In animal studies, tibolone and its derivatives are widely distributed in tissues after oral administration. Most is found in the liver, and high levels are also found in the kidneys. After repeated dosing, tibolone and its derivatives did not accumulate in tissues/15/.
Tibolone is metabolised by a first-pass effect. It is mainly metabolised in the liver, but metabolism may also occur in the intestine. 60-65% of the drug and its metabolites is excreted in the faeces. In humans, the elimination half-life of tibolone is = 45 hours. After a single dose, the elimination half-life of the hydroxy metabolites is = 6 hours/15/.
Pharmacodynamics (Cancer):
Preclinical studies: a study compared the dose-response effect (5 x 10 sup(-8) to 5 x 10 sup(-5)mol/L) of tibolone and its metabolites (Org OM38, Org 4094, and Org 30,126) on the sulfatase pathway of 2 hormone-dependent human breast cancer cells MCF-7 and T-47D. After 24h incubation with estrone sulfate 5 x 10

sup(-9)mol/L and high doses (5 x 10 sup(-5) and 5 x 10 sup(-6)mol/L) of the different compounds, the conversion of estrone sulfate to estradiol was strongly inhibited by all 5 substances tested. When low doses (5 x 10 sup(-8) and 5 x 10 sup(-7) mol/L) were used, tibolone and the metabolites Org 4094 and Org 30,126 still potently inhibited the conversion of estrone sulfate to estradiol in both cells, but the effect was less intense with Org OM38. Norethisterone was the least potent anti-sulfatase agent tested/16/.

Pharmacodynamics (Ischaemic Heart Disease):

Clinical studies: tibolone 1.25 or 2.5 mg/day significantly decreased serum levels of high density lipoprotein cholesterol, apolipoprotein AI and total cholesterol vs placebo. Serum triglyceride levels were also significantly lowered vs placebo. Levels of plasminogen activator inhibitor antigen and tissue plasminogen activator, and plasminogen activator inhibitor activity were significantly decreased vs placebo/17/. In another study, tibolone significantly decreased triglyceride, lipoprotein(a), plasminogen and plasminogen activator inhibitor-1 levels/18/.

No significant associations were observed between either aortic compliance or blood pressure-corrected aortic compliance values, and body mass index, time since menopause or family history of cardiovascular disease/19/.

Pharmacodynamics (Musculoskeletal Disorders):

Clinical studies: administration of tibolone (1.25 or 2.5mg for 24 months) resulted in a significant placebo-adjusted increase from baseline of trabecular and phalangeal bone density, vs placebo. Both doses of tibolone significantly decreased the levels of alkaline phosphatase and phosphorus from baseline vs placebo. The 2.5mg dose of tibolone significantly decreased the hydroxyproline/creatinine and calcium/creatinine ratios vs placebo/20/. In the first year after discontinuation of tibolone treatment in these patients, there was an increased loss of trabecular bone density compared with placebo/21/.

Pharmacodynamics (Women's Health):

Effects on the breast: in postmenopausal women, treatment with tibolone 2.5 mg/day for up to 24 months resulted in minimal mammographic changes. However, women with no mammographic changes had a significantly higher increase in serum dehydroepiandrosterone (DHEAS) levels than in women with mammographic changes/22/. Another study also showed no significant changes in breast density after treatment with tibolone for >= 12 months, compared with estradiol/ nomegestrol/23/.

Effects on bone density: loss of trabecular bone density was significantly greater 1 year after discontinuation of treatment with tibolone in patients treated with either 1.25 or 2.5 mg/day doses of tibolone compared with placebo. However, loss of cortical bone density did not increase in this study of postmenopausal women/21/.

Effects on endometrium: endometrial features were examined in patients with vaginal bleeding during tibolone therapy. In 42/43 patients, the endometrium was atrophic. 16/17 patients with intracavitary lesions (polyps, fibroids, congenital abnormalities) experienced bleeding during tibolone treatment. One patient had endometrial hyperplasia/24/ .

Tibolone relieved symptoms of urogenital atrophy and was not associated with endometrial proliferation in women with symptoms of vaginal atrophy. Similar results were also reported after administration of conjugated estrogens/25/.

Uterine bleeding: 28% of postmenopausal women experienced uterine bleeding during treatment with tibolone for 1 year, compared with 59% of women being treated with estradiol/norethisterone/26/.

Other effects: tibolone 2.5 mg/day od for 1 year was associated with a significant reduction in HDL and a significant elevation in serum ApoB in 41 menopausal osteoporotic women. However, total cholesterol values did not change. An increase in body mass index was statistically significant/27/.

Tibolone significantly decreased the levels of triglycerides and fasting glucose from baseline in a study involving 11 healthy postmenopausal women/28/.
Treatment with tibolone increased beta-endorphine levels in menopausal women to premenopausal values, and improved parameters of mood/15/.
In a comparative phase II study in 62 postmenopausal women of mean age 50 years, oral tibolone 2.5mg for 6 months did not significantly affect concentrations of plasma homocysteine, which is an independent risk factor for cardiovascular diseases/29/.
Tibolone and its metabolites enhanced prolactin expression in human endometrial stromal cells/30/.

THERAPEUTIC TRIALS:
Cancer:
Breast cancer: one patient in a study involving 14 patients with breast cancer showed a partial response to treatment with tibolone. The response duration in this patient was seen in an axillary soft tissue mass and lasted for 24 weeks/31/.

Treatment of the hypoestrogenic state in patients with uterine leiomyoma: in patients with uterine leiomyoma, treatment with a **gonadotropin-releasing*** hormone** agonist frequently causes unpleasant adverse events because of the hypoestrogenic state induced. In 50 women with uterine leiomyoma, randomised to receive leuprorelin depot (3.75 mg/dose) monthly for 6 months +- tibolone, the administration of tibolone did not compromise the therapeutic efficacy of leuprorelin. Vasomotor symptoms were significantly reduced and bone loss prevented in recipients of combination therapy vs leuprorelin monotherapy/32/.
In postmenopausal women with uterine leiomyoma, tibolone treatment significantly decreased the incidence of irregular spotting and irregular bleeding vs treatment with conjugated estrogens and medroxyprogesterone acetate. However, the incidence of amenorrhoea was higher in the tibolone group, but the difference did not reach significance. Endometrial thickness in all patients after 12 months' treatment was similar to that at baseline/33/.
Ischaemic Heart Disease:
An open-label study involving 10 postmenopausal women with chronic stable angina pectoris and confirmed coronary artery disease found that tibolone appears to have anti-ischaemic properties that are similar to those of estrogen. The women had not taken hormone replacement therapy for the past 3 months. Baseline exercise tests were conducted and the women then received oral tibolone 2.5mg, followed by exercise tests 24 hours later. 30 minutes' rest preceded each exercise test. Tibolone administration was associated with a significant improvement in time to onset of myocardial ischaemia (as defined by ST segment depression); the median time to onset was increased by 102 seconds, compared with baseline. The researchers concluded that a placebo-controlled study in a larger population is warranted/34/.
Musculoskeletal Disorders:
Dosage and administration: tibolone is administered as an oral dose once daily. The optimal dose for tolerability and efficacy is 2.5 mg/day.

Treatment of postmenopausal osteoporosis: tibolone 2.5 mg/day bid for 2 years significantly increased trabecular and cortical bone mineral density in 107 postmenopausal osteoporotic women. Lumbar spine bone mineral density increased by an average of 7.2% in tibolone recipients compared with 0.9% in placebo recipients, and by 8.9% in tibolone recipients with previous fractures. Femoral neck bone mineral density increased by 2.6% in tibolone recipients and 1.1% in tibolone recipients with previous fractures, and decreased by 1.6% in placebo recipients/35/. Eighty-eight women with symptomatic osteoporosis were randomised to receive oral tibolone 2.5 mg/day or placebo for 2 years in a double-blind study. After 24 months' therapy, the bone mineral density of the lumbar spine and the femoral neck had increased significantly from baseline in

tibolone, compared with placebo, recipients. The urinary calcium:creatinine ratio and the hydroxyproline:creatinine ratio decreased among tibolone recipients, indicating inhibition of bone resorption. Serum alkaline phosphatase and serum phosphate levels, both markers of bone formation, were also significantly reduced among tibolone, compared with placebo, recipients/12/.

In an open-label study, 47 postmenopausal women with normal mineral bone density (BMD) of the lumbar spine and femur were randomised to receive oral tibolone 2.5 mg/day (n = 26), or no treatment, for 96 weeks. BMD at the neck of the femur and Ward's triangle in tibolone-treated recipients did not significantly change from baseline over the entire study period. However, significant increases from baseline were recorded in the BMD of the lumbar spine from week 24 (+2.34% increasing to +3.67% at week 96), and of the trochanter at week 72 (+3.83%) and week 96 (+3.67%); these differences were significant compared with untreated controls/36/.

A study involving 94 women with postmenopausal osteoporosis, found that fluoride + tibolone was significantly more effective at increasing bone mineral density at the lumbar spine than fluoride + placebo. Lumbar spine bone mineral density increased without concurrent loss of cortical bone/37/.

Prevention of osteoporosis in postmenopausal women: both tibolone and estradiol/norethisterone increased the change in lumbar bone mineral density in postmenopausal women, compared with placebo. 81% of tibolone recipients were still compliant with treatment at 1 year, compared with 65% of patients in the estradiol/norethisterone group/38/. After 1 year, tibolone significantly increased bone mineral density compared with baseline and controls. Similar results were achieved with estradiol or estradiol + androgens/39/.

In a study involving 222 postmenopausal women that received treatment with tibolone or estradiol/norethisterone, bone mineral density increased in the lumbar spine and femur in all treatment groups/40/.

A meta-analysis of 2 phase III studies investigating the efficacy and tolerability of tibolone for the prevention of postmenopausal women found that tibolone 1.25 or 2.5mg increased spine and femur bone mineral density. Biochemical markers of bone turnover decreased at all time points in all treatment groups, and were significantly different from placebo after 2 years/41/.

In March 2002, research presented during an international expert meeting confirmed tibolone's (Livial sup((R))'s) advantages over conventional estrogen-containing hormone replacement therapies. Tibolone is licensed for the treatment of climacteric complaints and the prevention of osteoporosis in postmenopausal women. Clinical trials have confirmed that it is as effective as conventional treatment in alleviating climacteric complaints and may preserve bone mass to the same extent, however, tibolone has shown a number of important differences compared with conventional HRT. Clinical studies have shown that it has superior effects on women's mood and sexual well being. New results from a comparative study involving >500 women showed a significantly lower incidence of breast pain and vaginal bleeding and lower discontinuation rates, than treatment with continuous combined estrogen/progestogen. Results from another study showed that almost 60% of women continued tibolone treatment for at least 8 years - an unprecedented adherence rate that contrasts with that seen with conventional therapies. Observations that tibolone did not increase breast density were also confirmed by results from a double-blind, randomized controlled study. Tibolone did not reduce the sensitivity of mammography screening and is an important advantage compared to conventional HRT/42/.

Long-term treatment: in a randomised study involving 110 postmenopausal women with raised gonadotropin levels, open-label treatment with tibolone 2.5 mg/day for 10 years increased mean bone mineral density in treated women, compared with untreated control patients. Tibolone was associated with a significant improvement in mean lumbar spine and femoral neck bone mineral density at 10 years in postmenopausal women (+4.8 and +3.7%, respectively, vs baseline),

while untreated controls had significant reductions (-8.5 and -8.9%; p < 0.001). Tibolone was also associated with a reduced incidence and intensity of hot flushes/14/.

Pharmacoeconomic studies: a Markov model using previously published clinical data, healthcare resource-use estimates provided by an expert panel, and national cost data, was used to compare the costs and outcomes associated with the first 48 weeks of treatment with tibolone and estradiol/norethisterone in postmenopausal women with climacteric symptoms. It was found that for a mean additional cost of Lstg 21/patient, tibolone treatment (total cost Lstg 260/patient) was as effective as estradiol/norethisterone (Lstg 239/patient) at relieving climacteric symptoms in postmenopausal women. In addition, significant reductions in vaginal bleeding (-36%) and breast tenderness (-57%) were reported following tibolone use, compared with estradiol/ norethisterone treatment. The comparatively high acquisition cost of tibolone, compared with estradiol/norethisterone (Lstg 140 vs Lstg 85 per patient), was offset by the higher incidence of estradiol/ norethisterone-related adverse events, which in turn resulted in a higher HRT continuation rate among tibolone recipients/43/.

Postmenopausal osteoporosis in patients with rheumatoid arthritis: in a study involving 65 patients with rheumatoid arthritis and reduced bone mineral density, tibolone significantly increase bone mineral density at the femoral neck but not at the lumbar spine vs controls. Etidronic acid did significantly increase bone mineral density at the lumbar spine vs controls/44/.

Women's Health:

Dosage and administration: tibolone is administered as an oral dose once daily. The optimal dose for tolerability and efficacy is 2.5 mg/day/45/.

Premenstrual syndrome: treatment with tibolone 2.5 mg/day PO for 3 months significantly improved visual linear analogue scale scores and improved beta-endorphin concentrations versus placebo, in a study in 18 patients/46/.

Menopausal syndrome: in a study in 235 patients randomised to treatment with tibolone or **estradiol valerate**/norethisterone for 12 months, both treatments were found to have similar efficacy for relieving menopausal symptoms. However, **estradiol valerate**/ northisterone improved the high density lipoprotein to low density lipoprotein (HDL/LDL) cholesterol ratio, whereas tibolone significantly reduced HDL cholesterol but had no significant effect on the reduction of LDL cholesterol/10/. In a 48-week study in 423 women with menopausal symptoms, tibolone was associated with fewer adverse events than a combination of estradiol/norethisterone. Vaginal bleeding occurred significantly less often with tibolone than with estradiol/norethisterone. In addition, amenorrhoea was achieved more quickly with tibolone than with estradiol/norethisterone. The mean reduction from baseline in the score rating hot flushes among 423 evaluable women with menopausal symptoms was slightly but significantly greater with estradiol/norethisterone 2mg/1mg than with tibolone 2.5 mg/day/9/.

In a study in 210 postmenopausal women, tibolone was effective in relieving menopausal symptoms, particularly mood disorders and loss of libido, in most patients/47/.

Tibolone (2.5 mg/day) was at least as effective as estradiol (50 microg/day) in alleviating menopausal symptoms in a study in 76 women with surgical menopause. Vasomotor symptoms were reduced in 22/23 tibolone recipients and 26/29 receiving estradiol. Backache and arthralgia were reduced in 10/19 tibolone recipients and 9/26 in the estradiol group. Both psychological problems and sexual behaviour were improved in significantly more patients in the tibolone group (13/17 and 10/11, respectively) than in the estradiol group (9/21 and 7/15, respectively). Improvements in total cholesterol and triglyceride levels were also significantly greater in tibolone recipients/11/.

Both tibolone and continuous combined hormone replacement therapy improved

overall quality of life and wellbeing among postmenopausal women, according to results of an international study of 501 such women aged < 65 years who had not undergone hysterectomy and who were randomised to receive oral tibolone 2.5mg (n = 250) or oral conjugated estrogens (Premarin) 0.625mg plus oral medroxyprogesterone (Provera) 5mg for a 12-month period. Tibolone was associated with significantly less vaginal bleeding during cycles four-six than conjugated estrogens/medroxyprogesterone. However, tibolone and conjugated estrogens/medroxyprogesterone both improved quality of life, climacteric symptoms and urogenital symptoms in postmenopausal women/48/.

Female sexual dysfunction: in a study in 120 patients randomised to treatment with tibolone, estradiol or **estradiol valerate** + androgens, the frequency of sexual interest, frequency of orgasm, frequency of dyspareunia, general sexual satisfaction and sexual responsiveness were all significantly improved compared with untreated controls. The frequency of orgasm and sexual responsiveness were improved to a significantly greater extent in patients who received **estradiol valerate** + androgens or tibolone, compared with estradiol alone/39/.

Pharmacoeconomic studies: an economic appraisal found that tibolone improves quality of life for women with menopausal symptoms at `reasonable cost', according to a UK study. Based on data from published studies over a 5-year period, the researcher estimated that tibolone generates 0.05-0.11 quality-adjusted life-years (QALYs) in women with mild symptoms and 0.11-0.25 QALYs in those with severe symptoms, compared with continuous combined hormone replacement therapy. The cost/QALY gained was estimated to be Lstg 1180-6500 (discounted values). Compared with no hormone replacement therapy, the cost-QALY gained using tibolone also falls within an acceptable range. These cost values are based on the alleviation of menopausal symptoms and do not take into account the reduced risk of hip fracture, which would produce further QALY gains/49/.

Treatment of postmenopausal osteoporosis: tibolone 2.5 mg/day bid for 2 years significantly increased trabecular and cortical bone mineral density in 107 postmenopausal osteoporotic women. Lumbar spine bone mineral density increased by an average of 7.2% in tibolone recipients compared with 0.9% in placebo recipients, and by 8.9% in tibolone recipients with previous fractures. Femoral neck bone mineral density increased by 2.6% in tibolone recipients and 1.1% in tibolone recipients with previous fractures, and decreased by 1.6% in placebo recipients/35/. Eighty-eight women with symptomatic osteoporosis were randomised to receive oral tibolone 2.5 mg/day or placebo for 2 years in a double-blind study. After 24 months' therapy, the bone mineral density of the lumbar spine and the femoral neck had increased significantly from baseline in tibolone, compared with placebo, recipients. The urinary calcium:creatinine ratio and the hydroxyproline:creatinine ratio decreased among tibolone recipients, indicating inhibition of bone resorption. Serum alkaline phosphatase and serum phosphate levels, both markers of bone formation, were also significantly reduced among tibolone, compared with placebo, recipients/12/.

In an open-label study, 47 postmenopausal women with normal mineral bone density (BMD) of the lumbar spine and femur were randomised to receive oral tibolone 2.5 mg/day (n = 26), or no treatment, for 96 weeks. BMD at the neck of the femur and Ward's triangle in tibolone-treated recipients did not significantly change from baseline over the entire study period. However, significant increases from baseline were recorded in the BMD of the lumbar spine from week 24 (+2.34% increasing to +3.67% at week 96), and of the trochanter at week 72 (+3.83%) and week 96 (+3.67%); these differences were significant compared with untreated controls/36/.

In March 2002, research presented during an international expert meeting confirmed tibolone's (Livial sup((R))'s) advantages over conventional

estrogen-containing hormone replacement therapies. Tibolone is licensed for the treatment of climacteric complaints and the prevention of osteoporosis in postmenopausal women. Clinical trials have confirmed that it is as effective as conventional treatment in alleviating climacteric complaints and may preserve bone mass to the same extent, however; tibolone has shown a number of important differences compared with conventional HRT. Clinical studies have shown that it has superior effects on women's mood and sexual well being. New results from a comparative study involving >500 women showed a significantly lower incidence of breast pain and vaginal bleeding and lower discontinuation rates, than treatment with continuous combined estrogen/progestogen. Results from another study showed that almost 60% of women continued tibolone treatment for at least eight years - an unprecedented adherence rate that contrasts with that seen with conventional therapies. Observations that tibolone did not increase breast density were also confirmed by results from a double-blind, randomized controlled study. Tibolone did not reduce the sensitivity of mammography screening and is an important advantage compared to conventional HRT/42/.

Long-term treatment: in a randomised study involving 110 postmenopausal women with raised gonadotropin levels, open-label treatment with tibolone 2.5 mg/day for 10 years increased mean bone mineral density in treated women, compared with untreated control patients. Tibolone was associated with a significant improvement in mean lumbar spine and femoral neck bone mineral density at 10 years in postmenopausal women (+4.8 and +3.7%, respectively, vs baseline), while untreated controls had significant reductions (-8.5 and -8.9%; $p < 0.001$). Tibolone was also associated with a reduced incidence and intensity of hot flushes/14/.

Treatment of endometriosis: tibolone may be a therapeutic option for patients with residual endometriosis after undergoing bilateral oopherectomy with or without hysterectomy according to the results of a study conducted in Italy. In the study, 21 such patients were randomised to receive transdermal estradiol 0.05 mg/day, plus medroxyprogesterone 10 mg/day for 12 days per month, if they had not undergone hysterectomy (10), or tibolone 2.5 mg/day. Patients were followed-up for 12 months. Moderate pelvic pain was experienced by 4 estradiol recipients and 1 tibolone recipient during treatment. No patients experienced severe pelvic pain. One estradiol recipient reported severe dyspareunia; 2 patients in each treatment group experienced mild dyspareunia during treatment/50/.

In a Turkish study, tibolone ameliorated hypoestrogenic symptoms induced by goserelin therapy in women with endometriosis. Women with endometriosis who were receiving SC depot injections of goserelin 3.6mg every 4 weeks for 6 months were randomised to receive oral tibolone 2.5 mg/day (n = 15) or an iron pill (14). Treatment with tibolone or iron commenced at the beginning of the third menstrual cycle after starting goserelin therapy. After 3 months' therapy with goserelin alone, both treatment groups reported an increased frequency of vasomotor symptoms such as hot flushes, sweating and nervousness. After the addition of tibolone or iron, the incidence and severity of these symptoms was significantly reduced in tibolone, compared with iron, recipients. Similarly, while the urinary calcium:creatinine ratio increased during therapy with goserelin alone, tibolone recipients demonstrated a significant reduction in the urinary calcium:creatinine ration, compared with iron recipients/51/

DEVELOPMENT HISTORY:

27 Feb 2001	A study has been added to the adverse events and Women's Health therapeutic trials sections (855632)
31 Jan 2001	A pharmacoeconomic study has been added tot he Musculoskeletal Disorders therapeutic trials section (810917)
08 Jan 2001	Preregistration for Postmenopausal osteoporosis treatment in Japan (PO)
08 Jan 2001	Profile reviewed by Akzo Nobel
28 Jul 2000	Registered for Menopausal syndrome in Australia (PO)

28 Jul 2000 Registered for Menopausal syndrome in France (PO)
16 Feb 2000 Launched for Menopausal syndrome in Asia (PO)
16 Feb 2000 Launched for Menopausal syndrome in Latin America (PO)
16 Feb 2000 Launched for Postmenopausal osteoporosis prevention in Europe (PO)
16 Feb 2000 Launched for Postmenopausal osteoporosis prevention in Latin America (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Asia (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Brazil (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Italy (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Netherlands (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Scandinavia (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in South Africa (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in South America (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in Spain (PO)
25 Jan 2000 Launched for Postmenopausal osteoporosis prevention in United Kingdom (PO)
25 Jan 2000 Phase-III clinical trials for Postmenopausal osteoporosis treatment in Japan (PO)
25 Jan 2000 Preregistration for Menopausal syndrome in Canada (PO)
25 Jan 2000 Preregistration for Postmenopausal osteoporosis prevention in Canada (PO)
25 Jan 2000 Preregistration for Postmenopausal osteoporosis prevention in Europe (PO)
25 Jan 2000 Preregistration for Postmenopausal osteoporosis prevention in USA (PO)
18 Nov 1999 Launched for Menopausal syndrome in Germany (PO)
18 Nov 1999 Launched for Menopausal syndrome in World (PO)
18 Nov 1999 Launched for Postmenopausal osteoporosis in World (PO)
18 Nov 1999 Phase-III clinical trials for Menopausal syndrome in Japan (PO)
18 Nov 1999 Preregistration for Menopausal syndrome in USA (PO)
16 Nov 1999 Kanebo's pharmaceutical business has been merged with Organon's Japanese operations to form Nippon Organon
29 Oct 1999 A study in patients with residual endometriosis has been added to the Women's Health therapeutic trials section (797271)
29 Oct 1999 Investigation in Endometriosis in Italy (PO)
11 Oct 1999 Launched for Postmenopausal osteoporosis in Asia (PO)
11 Oct 1999 Launched for Postmenopausal osteoporosis in South America (PO)
21 Sep 1999 Launched for Menopausal syndrome in Scandinavia (PO)
21 Sep 1999 Launched for Postmenopausal osteoporosis in Scandinavia (PO)
09 Sep 1999 Launched for Postmenopausal osteoporosis in Europe (PO)
09 Sep 1999 Preregistration for Postmenopausal osteoporosis in Canada (PO)
09 Sep 1999 Preregistration for Postmenopausal osteoporosis in USA (PO)
06 Sep 1999 A study in postmenopausal women with osteoporosis has been added to the Musculoskeletal Disorders and Women's Health therapeutic trials sections (779944)
30 Apr 1999 A clinical study of bone density loss has been added to the Women's Health pharmacodynamics section (748139)
29 Oct 1998 A study in women with osteoporosis has been added to the adverse events and the Musculoskeletal Disorders and Women's Health therapeutic trials sections (714153)
15 Sep 1998 A study has been added to the Women's Health therapeutic trials section (698900)
18 Aug 1998 A study has been added to the Women's Health therapeutic trials section (691857)

15 Jul 1998 Launched for Menopausal syndrome in Brazil (PO)
30 Jun 1998 Phase-III clinical trials for Postmenopausal osteoporosis in Japan (PO)
30 Jun 1998 Profile reviewed by Kanebo
22 Jun 1998 A clinical study has been added to the Women's Health pharmacodynamics section (672800)
04 Jun 1998 Launched for Menopausal syndrome in Spain (PO)
02 Dec 1997 Phase-III clinical trials for Postmenopausal osteoporosis in USA (PO)
23 Jun 1997 Preclinical development for Breast cancer in France (PO)
23 Jun 1997 Preclinical development for Breast cancer in Netherlands (PO)
25 Feb 1997 Launched for Menopausal syndrome in Italy (PO)
25 Feb 1997 Launched for Menopausal syndrome in South Africa (PO)
25 Feb 1997 Phase-III clinical trials for Postmenopausal osteoporosis in Europe (PO)
20 Feb 1997 Launched for Menopausal syndrome in Europe (PO)
20 Feb 1997 Launched for Menopausal syndrome in Netherlands (PO)
20 Feb 1997 New profile
20 Feb 1997 Phase-II clinical trials for Postmenopausal osteoporosis in Japan (PO)
20 Feb 1997 Phase-II clinical trials for Postmenopausal osteoporosis in USA (PO)

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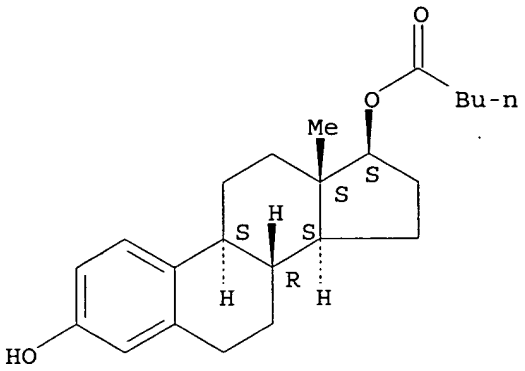
L170 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:978863 CAPLUS
DOCUMENT NUMBER: 144:143261
TITLE: A study of the control of climacteric symptoms in postmenopausal women following sequential regimens of 1 mg 17β-estradiol and trimegestone compared with a regimen containing 1 mg estradiol valerate and norethisterone over a 2-year period
AUTHOR(S): Pornel, B.; Spielmann, D.
CORPORATE SOURCE: The Trimegestone 302 Study Group, Brussels Menopause Center, Brussels, Belg.
SOURCE: Gynecological Endocrinology (2005), 21(2), 74-81
CODEN: GYENER; ISSN: 0951-3590
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 08 Sep 2005
AB Objective: To compare the efficacy of two sequential 17β-estradiol (17β-E2)/trimegestone (TMG) combinations with the sequential estradiol valerate (E2V)/norethisterone (NET) regimen in relieving climacteric symptoms. Study design: This was a double-blind, randomized, multicenter study conducted among 1218 Caucasian (99%) postmenopausal women with an intact uterus in seven European countries and Israel, over 13 cycles (each of 28 days). Study duration was extended further for 13 cycles, with 531 women receiving treatment for up to 26 cycles. Treatments consisted of 1 mg 17β-E2 on days 1-14 and 1 mg 17β-E2/0.125 mg TMG or 0.25 mg TMG on days 15-28, and 1 mg E2V on days 1-16 and 1 mg E2V/1 mg NET on days 17-28. Results: Rapid and significant redns. in the mean daily number and severity of hot flushes and in the mean daily number of nocturnal sweats were established in most women with 1 mg 17β-E2/0.25 mg TMG and E2V/NET. These treatments also induced a significant improvement in the quality-of-life assessments. Conclusion: The 1 mg 17β-E2/0.25 mg TMG regimen provides rapid and effective relief of menopausal symptoms, with a reduction in the number of hot flushes at least as good as' that of the E2V/NET comparator.
IT **979-32-8**, Estradiol valerate
RL: **ADV (Adverse effect, including toxicity)**; BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(combination therapy of 17β-estradiol and trimegestone reduced number and severity of **hot flushes** as good as E2V/NET treatment and reduced number of nocturnal sweats, improved kupperman index and quality of life in postmenopausal woman)
RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

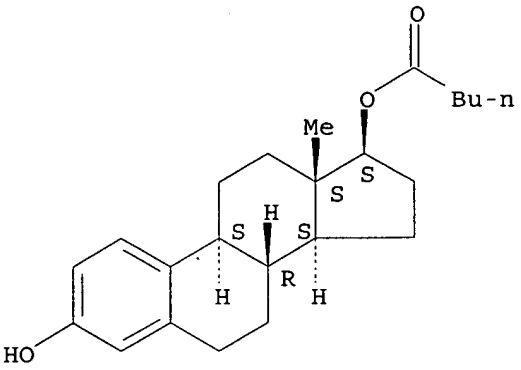
L170 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1022315 CAPLUS
DOCUMENT NUMBER: 142:191433
TITLE: Smoking reduces **breast tenderness** during oral estrogen-progestogen therapy
AUTHOR(S): Bjarnason, Nh; Jorgensen, C.; Kremmer, H.; Alexandersen, P.; Christiansen, C.
CORPORATE SOURCE: Center for Clinical & Basic Research, Ballerup, 2750, Den.
SOURCE: Climacteric (2004), 7(4), 390-396
CODEN: CLIMFC; ISSN: 1369-7137
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 Nov 2004
AB The authors wished to study the influence of smoking upon the occurrence of breast tenderness during oral estrogen-progestogen therapy (EPT). Data from 626 healthy postmenopausal women participating in three double-blind, randomized, controlled long-term trials of EPT vs. placebo were included. The studies covered sequential, continuous and interrupted regimens of estradiol opposed by a selection of progestins. All studies were mono-center studies and performed in the period 1988-1997. Data on breast tenderness were collected from adverse event reporting and information on smoking status was obtained by interview. Smoking was associated with an earlier age at menopause (difference: 1.3 years) and a slightly lower body mass index (difference: 0.8 kg/m2). Smoking women in the EPT groups had significantly lower on-treatment estradiol levels compared to non-smoking women, whereas no differences were observed in the placebo group. In parallel, the incidence of breast tenderness during EPT was reduced by about one-half in smokers compared to non-smokers, whereas no differences were seen on placebo. Thus, current smoking reduces the incidence of breast tenderness in women receiving oral EPT. This may be caused by the increased degradation of estradiol during smoking.
IT **60513-93-1**, Estradiol valerate-levonorgestrel mixture
64368-84-9, Estradiol valerate-medroxyprogesterone acetate mixture
108116-22-9, Estradiol valerate-cyproterone acetate mixture
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(smoking reduction of **breast tenderness** during oral estrogen-progestogen therapy in postmenopausal women)

RN 60513-93-1 CAPLUS
CN 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 979-32-8
CMF C23 H32 O3

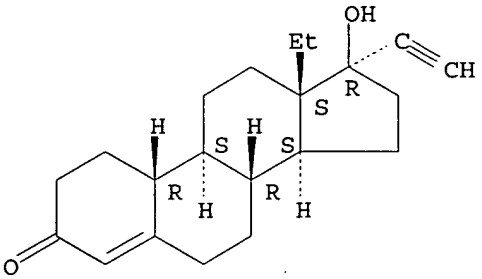
Absolute stereochemistry.



CM 2

CRN 797-63-7
CMF C21 H28 O2

Absolute stereochemistry.

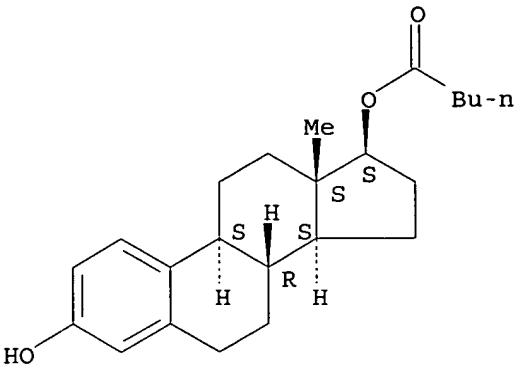


RN 64368-84-9 CAPLUS
CN Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 979-32-8
CMF C23 H32 O3

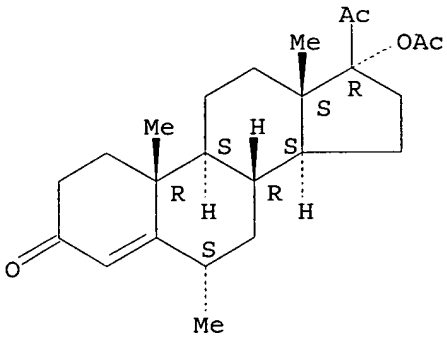
Absolute stereochemistry.



CM 2

CRN 71-58-9
CMF C24 H34 O4

Absolute stereochemistry.

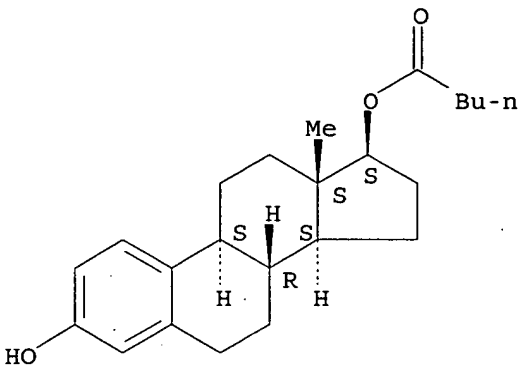


RN 108116-22-9 CAPLUS
CN 3'H-Cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione, 17-(acetyloxy)-6-chloro-1,2-dihydro-, (1β,2β)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 979-32-8
CMF C23 H32 O3

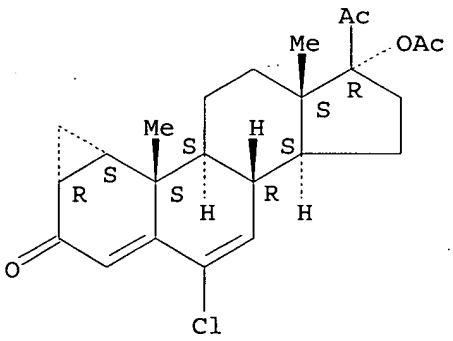
Absolute stereochemistry.



CM 2

CRN 427-51-0
CMF C24 H29 Cl O4

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:830564 CAPLUS
DOCUMENT NUMBER: 142:980
TITLE: Relationship between allopregnanolone and negative mood in postmenopausal women taking sequential hormone replacement therapy with vaginal progesterone
AUTHOR(S): Andreen, Lotta; Sundstroem-Poromaa, Inger; Bixo, Marie; Andersson, Agneta; Nyberg, Sigrid; Baeckstroem, Torbjoern
CORPORATE SOURCE: Umea Neurosteroid Research Center, Department of Clinical Science, Obstetrics and Gynecology, Norrlands University Hospital, Umea, SE-901 85, Swed.
SOURCE: Psychoneuroendocrinology (2004), Volume Date 2005, 30(2), 212-224
CODEN: PSYCDE; ISSN: 0306-4530
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 Oct 2004

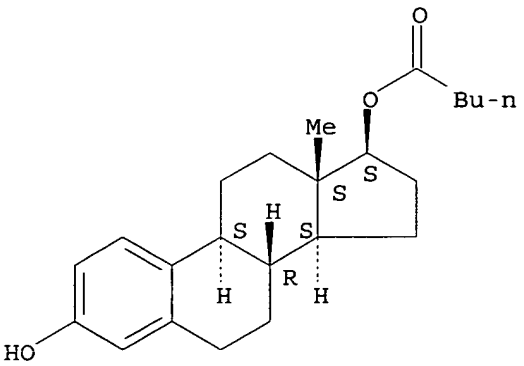
AB Objective: To compare severity of neg. mood and phys. symptoms between women with different progesterone, allopregnanolone, and pregnanolone plasma concns. during sequential Hormone Replacement Therapy (HRT) with vaginal progesterone suppositories. Design: A randomized, placebo-controlled, double-blind, crossover study. Postmenopausal women (n=36) with climacteric symptoms were treated with 2 mg estradiol daily during 3 28-day cycles. Vaginal progesterone suppositories with 400, 800 mg/day or placebo were added sequentially for 14 days per cycle. Daily symptom ratings using a validated rating scale were kept. Blood samples for progesterone, allopregnanolone, and pregnanolone RIAs were collected during each treatment cycle. Women were divided into 3 groups (low, medium, and high) based on plasma allopregnanolone concentration during progesterone treatment. The concentration of allopregnanolone in the medium group corresponds to the concentration seen during the mid luteal phase of the menstrual cycle. Within women with medium allopregnanolone concentration significantly more neg. mood and phys. symptoms were rated during progesterone treatment compared to treatment with unopposed estrogen or placebo. Between women significantly more neg. mood symptoms were seen during progesterone treatment cycles with medium allopregnanolone concentration compared to cycles with low concentration Plasma progesterone, allopregnanolone, and pregnanolone concns. increased with increasing progesterone dose. Progesterone and allopregnanolone plasma concns. increased 2 h after vaginal administration of progesterone at 400 and 800 mg/day. Vaginal progesterone in sequential HRT causes neg. mood, most likely mediated via allopregnanolone.

IT **979-32-8**, Estradiol valerate
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(relationship between allopregnanolone and neg. mood in postmenopausal women taking sequential hormone replacement therapy with vaginal progesterone)

RN 979-32-8 CAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:770465 CAPLUS
DOCUMENT NUMBER: 141:420546

TITLE: Influence of a continuous combined HRT (2 mg estradiol valerate and 2 mg dienogest) on postmenopausal depression

AUTHOR(S): Rudolph, I.; Palombo-Kinne, E.; Kirsch, B.; Mellinger, U.; Breitbarth, H.; Graeser, T.

CORPORATE SOURCE: Jenapharm GmbH & Co. KG, Jena, Germany

SOURCE: Climacteric (2004), 7(3), 301-311
CODEN: CLIMFC; ISSN: 1369-7137

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 22 Sep 2004

AB Objective: This randomized, double-blind, placebo-controlled study was planned to investigate the effects of continuous combined hormone replacement therapy (HRT) with 2 mg estradiol valerate and 2 mg dienogest (Climodien/Lafamme) over 24 wk on postmenopausal depression. Method: A total of 129 patients with a mild to moderate depressive episode according to ICD-10: F32.0, F32.1 in the context of a postmenopausal syndrome (ICD-10: N95.1) and a baseline score in the Hamilton depression scale (HAMD) ≥ 16 were included in the study. The primary target variable was depression severity as measured by the HAMD after 24 wk of treatment. A four-point difference between HRT and placebo at the end of the study and, in addition, a final score ≤ 8 (corresponding to an improvement of ≥ 50% as compared to baseline) for the individual patient (responders anal.) were considered clin. relevant. Clin. global impression (CGI) of investigators (therapeutic and side-effects) at the end of the study was investigated. Secondary effects of HRT on depression severity caused by its effect on vasomotor symptoms or sleep disturbances (domino hypothesis) were taken into consideration. Also, the study addressed the question of whether the effect of HRT on depression severity depends on a history of premenstrual syndrome (PMS) or postnatal depression (PND). Results: The results showed a clear and clin. relevant reduction of depression severity under HRT after 24 wk of treatment and superiority over placebo ($p < 0.0005$) in spite of a strong placebo effect. The effects of the estrogen-progestin combination thereby seemed only partially to be dependent on the improvement of vasomotor symptoms and sleep disturbances. Also, the effects of HRT could not be shown to be dependent on a history of PMS and/or PND, even though women with and without this history clearly differed in baseline depression scores ($p < 0.0001$). The assessment of CGI was pos.: whereas HRT was clearly superior to placebo with regard to therapeutic effects ($p = 0.0014$), there were no differences with regard to side-effects ($p = 0.35$). Conclusion: The combination of 2 mg estradiol valerate and 2 mg dienogest can be regarded as an effective and safe treatment option for women with mild to moderate depression in the context of postmenopausal syndrome.

IT **307334-58-3**, Climodien
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(influence of a continuous combined hormone replacement therapy (2 mg estradiol valerate and 2 mg dienogest) on postmenopausal depression)

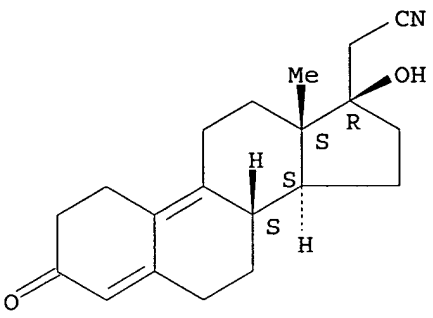
RN 307334-58-3 CAPLUS

CN 19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-, (17α)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 65928-58-7
CMF C20 H25 N O2

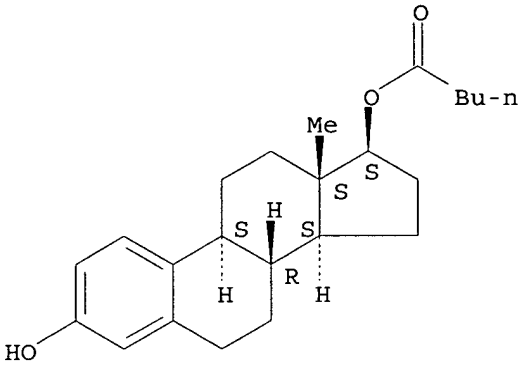
Absolute stereochemistry.



CM 2

CRN 979-32-8
CMF C23 H32 O3

Absolute stereochemistry.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

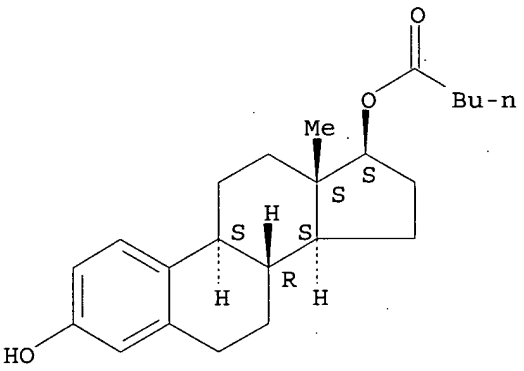
L170 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:967688 CAPLUS
DOCUMENT NUMBER: 140:229672
TITLE: Clinical experience with trimegestone as a new progestin in HRT
AUTHOR(S): Grubb, Gary; Spielmann, Daniele; Pickar, James; Constantine, Ginger
CORPORATE SOURCE: Women's Health Clinical Research and Development, Collegeville, PA, 19426, USA
SOURCE: Steroids (2003), 68(10-13), 921-926
CODEN: STEDAM; ISSN: 0039-128X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 11 Dec 2003
AB Trimegestone (TMG) is a novel, 19-norpregnane progestin, which demonstrates endometrial selectivity with a reduced progestin-related side effect profile when compared to several other currently marketed

progestins. TMG has been studied in combination with 17β-estradiol (17β-E2) and conjugated equine estrogens (CEE). TMG-containing HRT agents were effective in relieving vasomotor symptoms and providing protection from endometrial hyperplasia with ≤1% hyperplasia. In clin. trials with sequential regimens, TMG provided predictable withdrawal bleeding associated with a low incidence of irregular and prolonged bleeding. Clin. studies of continuous combined regimens of estrogen/TMG combinations demonstrated high levels of amenorrhea. Both 17β-E2 and CEE/TMG combinations have shown improved bone mineral d. and quality-of-life assessments. Both continuous combined and sequential regimens of 17β-E2/TMG and CEE/TMG have a favorable clin. profile. TMG provides an important new option for the treatment of postmenopausal symptoms and the prevention of osteoporosis.

IT **979-32-8**, Estradiol valerate **282089-44-5**, Cyclocur
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(comparison with trimegestone treatment; clin. experience with trimegestone as a new progestin in hormone replacement therapies)

RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.

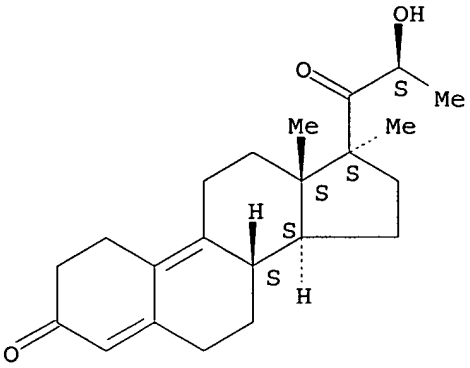


RN 282089-44-5 CAPLUS
CN Estra-4,9-dien-3-one, 17-[(2S)-2-hydroxy-1-oxopropyl]-17-methyl-, (17β)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 74513-62-5
CMF C22 H30 O3

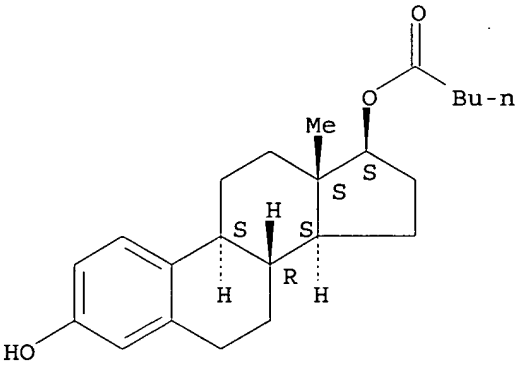
Absolute stereochemistry.



CM 2

CRN 979-32-8
CMF C23 H32 O3

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:808004 CAPLUS
DOCUMENT NUMBER: 140:175349
TITLE: Vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy: preliminary results
AUTHOR(S): Navarro, Paula Andrea de A. S.; Kaddouz, Delphine; De Ziegler, Dominique; Silva De Sa, Marcos Felipe; Ferriani, Rui Alberto
CORPORATE SOURCE: Faculty of Medicine of Ribeirao Preto, Department of Gynecology and Obstetrics, University of Sao Paulo, Ribeirao Preto, Brazil
SOURCE: Maturitas (2003), 46(2), 147-152
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Oct 2003

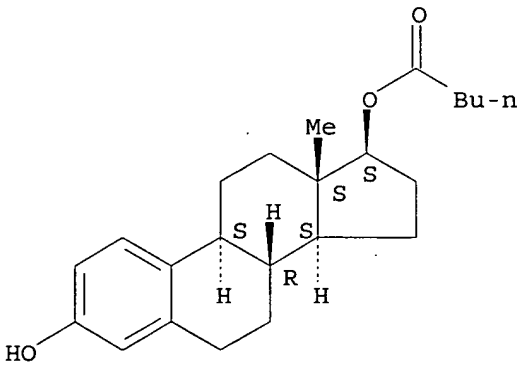
AB Objective: To assess the tolerability and endometrial effects of vaginal administration of an allopregnanolone gel to postmenopausal women undergoing estrogen therapy. Methods: Thirteen postmenopausal women included in the study were divided into two groups and submitted to two consecutive cycles of 28 days during which they received 2 mg oral estradiol valerate daily and vaginally administered allopregnanolone gel during the last 10 days of the second cycle (group 1) or during the last 10 days of each cycle (group 2). Systemic adverse effects, vaginal bleeding and endometrial histol. were characterized, with group 1 patients being submitted to two endometrial biopsies (days 28 and 56) and group 2 patients to one biopsy (day 56). Results: Five patients did not show any adverse effect. Mastalgia was the most frequently reported adverse effect (four cases), followed by headache and abdominal pain (two cases each). The adverse effects were mild and did not interfere with the adequate use of the medication prescribed. Vaginal bleeding due to deprivation was observed in three of the seven patients submitted to one treatment cycle with allopregnanolone (group 1) and in two of six patients submitted to two treatment cycles (group 2). Endometrial biopsy findings did not suggest any secretory action after exposure to allopregnanolone. Conclusions: Tolerability of vaginal administration of allopregnanolone gel was good. Studies employing a larger series and longer time of follow-up are necessary to determine the endometrial effects of this drug.

IT **979-32-8**, Estradiol valerate
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(preliminary clin. study for vaginal administration of allopregnanolone to postmenopausal women undergoing estrogen replacement therapy)

RN 979-32-8 CAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

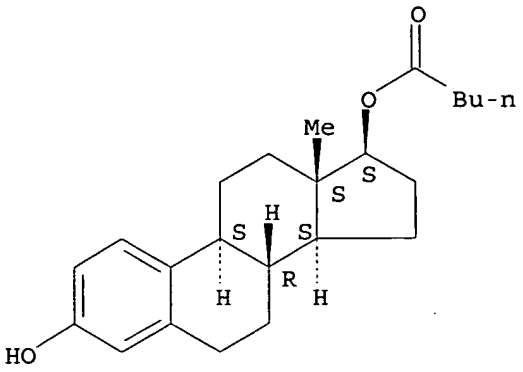
L170 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:463622 CAPLUS
DOCUMENT NUMBER: 137:57759
TITLE: Hormone replacement therapy: estrogen and progestin effects on plasma C-reactive protein concentrations
AUTHOR(S): Skouby, Sven O.; Gram, Jorgen; Andersen, Lars F.; Sidelmann, Johannes; Petersen, Kresten R.; Jespersen, Jorgen

CORPORATE SOURCE: Department of Obstetrics and Gynecology, Frederiksberg Hospital, Copenhagen, DK 2000, Den.
SOURCE: American Journal of Obstetrics and Gynecology (2002), 186(5), 969-977
CODEN: AJOGAH; ISSN: 0002-9378
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 21 Jun 2002

AB Our purpose was to assess the effect of hormone replacement therapy (HRT) on C-reactive protein blood concns. with special reference to the progestin component. Changes from baseline and between groups in blood concns. of C-reactive protein were determined during 12-mo periods in 6 groups of postmenopausal women. Group A (the reference group) received no HRT; group B received 2 mg of estradiol valerate (E2V) daily combined with 1 mg of cyproterone acetate (CPA) for 10 days (28/10 days); group C received 2 mg of E2V plus 1 mg of CPA sequentially (21/10 days); group D received a combination of 2 mg of E2V and 1 mg of norethindrone acetate continuously; group E received 2 mg of E2V in combination with local delivery of levonorgestrel (20 μg/24 h); and group F received a long-cycle regimen consisting of 2 mg of E2V (84/91 days) plus 20 mg of medroxyprogesterone (14/91 days). No significant variation in CRP levels was observed in the reference group. HRT resulted in a significant increase in CRP concns. in the women receiving the continuous combination of E2V plus norethindrone acetate and the continuous regimen of E2V plus local delivery of levonorgestrel. Cyclic or continuous intake of E2V plus CPA did not change CRP levels significantly. During the long-cycle regimen, the concns. of CRP showed a significant variance over time. The concns. increased during the estrogen phase but were modulated by the progestin intake throughout the study period. HRT can increase CRP levels in healthy women, and both the estrogen and the progestin component are of importance for the change. Whether the increase in CRP levels only reflects a changed steady-state metabolism is unknown. However, the clin. significance should be viewed from the perspective of changes in other inflammatory risk markers of importance for the evolution of cardiovascular disease.

IT **979-32-8**, Estradiol valerate
RL: **ADV (Adverse effect, including toxicity)**; THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(effects of estrogen and progestin replacement therapy on plasma C-reactive protein concns. in postmenopausal women)
RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:59967 CAPLUS
DOCUMENT NUMBER: 136:257440
TITLE: Climodien (estradiol valerate 2 mg plus dienogest 2 mg) is safe and effective in the treatment of postmenopausal complaints
AUTHOR(S): Graser, T.; Romer, T.; Wiedey, K. D.; Janaud, A.
CORPORATE SOURCE: Department of Drug Safety, Jenapharm GmbH and Co. KG, Jena, D-07745, Germany
SOURCE: Climacteric (2001), 4(4), 332-342
CODEN: CLIMFC; ISSN: 1369-7137
PUBLISHER: Parthenon Publishing Group Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Jan 2002
AB Objective: To evaluate the efficacy, safety and tolerability of continuous combined hormone replacement therapy (HRT) with Climodien (estradiol valerate 2 mg plus dienogest 2 mg). Design: Open, multinational, multicenter, non-controlled phase III study. Participants: A total of 1501 women aged 52-65 yr with postmenopausal symptoms of sufficient severity to require treatment. Eligible patients were treated with Climodien for 12 treatment cycles (48 wk), with assessments of efficacy, safety and tolerability (adverse events) at 8, 24 and 48 wk. Efficacy was assessed using the Kupperman index. Safety assessments included endovaginal sonog., safety endometrial biopsies, mammog., phys. and gynecol. examination, vital signs, prothrombotic factors and routine laboratory safety parameters. The Kupperman index improved with increasing duration of treatment, accompanied by an improvement in self-reported patient well-being. Individual climacteric symptoms such as hot flushes and psychonervous disorders also improved. The most pronounced improvement was seen in women who had not previously used HRT. The incidence of breakthrough bleeding declined over time, resulting in complete amenorrhea in 86.2% of the patients after 12 cycles of treatment. Furthermore, total and low-d. lipoprotein (LDL) cholesterol levels decreased and high-d. lipoprotein (HDL) cholesterol levels increased. Decreases in alkaline phosphatase, pyridinoline and deoxypyridinoline demonstrated the inhibitory action of estradiol on bone resorption. Endometrial thickness remained almost constant, and the incidence of serious endometrial findings was similar to that in untreated women. Continuous combined estrogen-progestin therapy with Climodien is effective, safe and well tolerated in postmenopausal women, with a profile and incidence of adverse

events consistent with those of existing HRT prepns.

IT **307334-58-3**, Climodien
RL: **ADV (Adverse effect, including toxicity)**; PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(climodien is safe and effective in treatment of postmenopausal complaints)

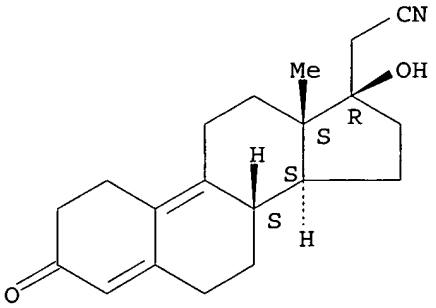
RN 307334-58-3 CAPLUS

CN 19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-, (17α)-, mixt. with (17β)-3-hydroxyestra-1,3,5(10)-trien-17-yl pentanoate (9CI) (CA INDEX NAME)

CM 1

CRN 65928-58-7
CMF C20 H25 N O2

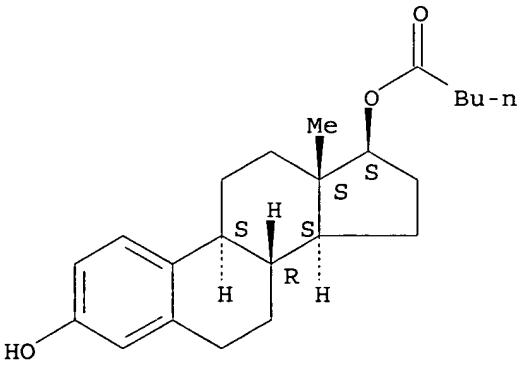
Absolute stereochemistry.



CM 2

CRN 979-32-8
CMF C23 H32 O3

Absolute stereochemistry.

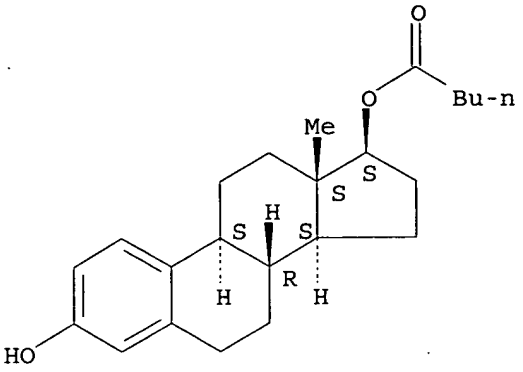


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:887821 CAPLUS

DOCUMENT NUMBER: 136:194384
TITLE: Low-dose estrogen supplementation improves vascular function in hypogonadal men
AUTHOR(S): Komesaroff, Paul A.; Fullerton, Meryl; Esler, Murray D.; Dart, Anthony; Jennings, Garry; Sudhir, Krishnankutty
CORPORATE SOURCE: Hormones and Vasculature Laboratory and Alfred and Baker Medical Unit, Baker Medical Research Institute and Alfred Hospital, Melbourne, Australia
SOURCE: Hypertension (2001), 38(5), 1011-1016
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Dec 2001
AB It is widely accepted that in women, estrogens provide protection against the development of cardiovascular disease. However, the cardiovascular role of estrogens in men remains uncertain, despite preliminary evidence that endogenous estrogens produced by aromatization of androgenic precursors are of physiol. importance. Hypogonadal men have very low levels of circulating estrogen. The authors studied the responsiveness of forearm resistance arteries to vasoconstrictor and vasodilator agents in 12 men (mean±SEM age, 68.7±2.6 yr) rendered hypogonadal as a result of treatment for prostatic cancer, before and after 8 wk of estrogen supplementation (estradiol valerate 1 mg daily; n=7) or placebo (n=5). Forearm blood flow was measured by venous occlusion plethysmog., and vasoactive agents were infused through a brachial artery cannula in doses that did not affect blood pressure or heart rate. Estrogen supplementation was well tolerated, with no adverse effects. After estrogen treatment, mean estradiol levels increased from <30 to 308±65 pmol/L, and both systolic and diastolic blood pressures were reduced. HDL cholesterol levels increased significantly, and vasoconstrictor responses to the NO synthase inhibitor NG-monomethyl-L-arginine (1, 2, 4 μmol/min) were enhanced. Vasoconstrictor responses to angiotensin II (8, 16, 32 ng/min) were markedly attenuated by estrogen treatment, as were vasoconstrictor responses to norepinephrine (25, 50, 100 ng/min). Estrogen did not alter the vasodilator responses to acetylcholine (9.25, 18.5, 37 μg/min) or to the endothelium-independent agent sodium nitroprusside (1.6 μg/min). Responses to all vasoactive agents were unchanged after administration of placebo. The authors conclude that low-dose estrogen supplementation in hypogonadal men is well tolerated, lowers blood pressure, and may affect vascular reactivity in a manner that is potentially beneficial, through several mechanisms, including enhancement of basal NO release and attenuation of vasoconstrictor responses to angiotensin II and norepinephrine. These findings suggest the need to consider a possible clin. role for estrogenic compds. in cardiovascular risk reduction in some groups of men.
IT **979-32-8**, Estradiol valerate
RL: **ADV (Adverse effect, including toxicity)**; DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(low-dose estrogen supplementation improves vascular function and reactivity to vasoactive agents in hypogonadal men)
RN 979-32-8 CAPLUS
CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L170 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:862323 CAPLUS
DOCUMENT NUMBER: 136:194378
TITLE: Effect of estradiol valerate alone or in association with cyproterone acetate upon vascular function of postmenopausal women at increased risk for **cardiovascular** disease
AUTHOR(S): Vitale, Cristiana; Fini, Massimo; Leonardo, Filippo; Rossini, Paola; Cerquetani, Elena; Onorati, Daniela; Rosano, Giuseppe M. C.
CORPORATE SOURCE: Cardiovascular Research Unit, Department of Internal Medicine, San Raffaele-TOSINVEST SANITA, Rome, 00163, Italy
SOURCE: Maturitas (2001), 40(3), 239-245
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 Nov 2001
AB A large body of evidence has been accumulated suggesting that impairment of vascular endothelial function is an initial step in the development of atherosclerosis. Recent studies have shown that estrogen replacement therapy in postmenopausal women (PMW) improves endothelium-dependent, flow-mediated dilatation (FMD) while the cyclical adjunct of a progestin may reverse this effect. The purpose of this study was to evaluate endothelium-dependent, FMD in the brachial artery and the plasma levels of Endothelin-1 in menopausal females treated with estradiol valerate with and without cyclical cyproterone acetate in 20 PMW (mean age 64 yr) with more than one risk factor for coronary artery disease. After a baseline evaluation, PMW entered a double-blinded, placebo controlled single cross-over study and were randomized to receive either estradiol valerate (2 mg) for 21 days or estradiol valerate (2 mg) for 11 days and estradiol valerate (2 mg) and cyproterone acetate (1 mg) for 10 days. Patients were crossed-over the complementary treatment 7 days after completing the first treatment phase. The study of forearm blood flow was repeated at the end of each treatment period. Estradiol valerate significantly increased FMD as compared with baseline (12 vs. 7%) the adjunct of cyproterone acetate did not affect the effect of estradiol valerate upon FMD (12 vs. 11%, P= NS). Similarly reactive hyperemic flow increased after estradiol valerate alone (24%) or in association with cyproterone acetate (24%) compared with baseline. Plasma levels of Endothelin-1 were significantly reduced by

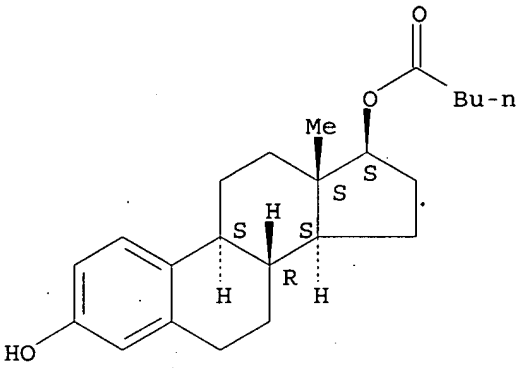
estradiol valerate alone or in association with cyproterone acetate. In conclusion hormone replacement therapy with estradiol valerate and cyproterone acetate improves endothelial function and reduces plasma levels of Endothelin-1 in PMW at risk of coronary artery disease. These effects may be relevant for cardioprotection.

IT **979-32-8**, Estradiol valerate
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); **USES (Uses)**
(effect of estradiol valerate alone or in association with cyproterone acetate upon vascular function of postmenopausal women at increased risk for **cardiovascular** disease)

RN 979-32-8 CAPLUS

CN Estra-1,3,5(10)-triene-3,17-diol (17β)-, 17-pentanoate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

FILE 'HOME' ENTERED AT 12:11:37 ON 02 MAR 2006

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L2             1 SEA FILE=REGISTRY ABB=ON  979-32-8
L3               STR
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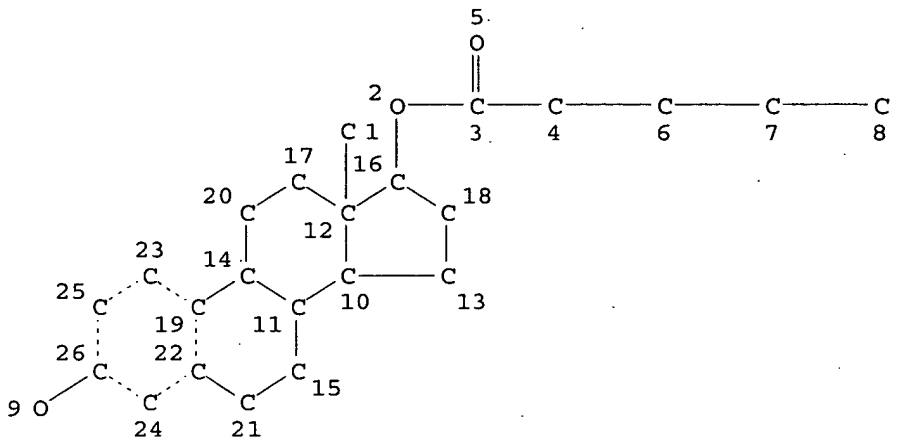

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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  26

STEREO ATTRIBUTES: NONE
L5            29 SEA FILE=REGISTRY FAM FUL L3
L6               SEL  L2 1- RN :       1 TERM
L7            25 SEA FILE=REGISTRY ABB=ON  L6/CRN
L9             4 SEA FILE=REGISTRY ABB=ON  L5 NOT L7
L11            2 SEA FILE=REGISTRY ABB=ON  L9 AND A
L12           27 SEA FILE=REGISTRY ABB=ON  L5 NOT L11



     (FILE 'HOME' ENTERED AT 10:43:25 ON 02 MAR 2006)

     FILE 'CAPLUS' ENTERED AT 10:43:36 ON 02 MAR 2006
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               SET NOTICE 1000 SEARCH
L1             2 SEA ABB=ON  US2003-729487/AP
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               SET LINE LOGIN
               SET DETAIL LOGIN
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     FILE 'REGISTRY' ENTERED AT 10:45:16 ON 02 MAR 2006
L2             1 SEA ABB=ON  979-32-8
               D SCAN

     FILE 'REGISTRY' ENTERED AT 10:45:36 ON 02 MAR 2006
               D IDE
L3             STR  979-32-8
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L4            0 SEA FAM SAM L3
L5           29 SEA FAM FUL L3
                SAVE TEMP L5 QAZ487FAM/A
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L6              SEL L2 1- RN :       1 TERM
                SET SMARTSELECT OFF
L7           25 SEA ABB=ON  L6/CRN
L8            0 SEA ABB=ON  L7 NOT L5
L9            4 SEA ABB=ON  L5 NOT L7
                D SCAN
L10          16 SEA ABB=ON  L5 NOT A
L11           2 SEA ABB=ON  L9 AND A
L12          27 SEA ABB=ON  L5 NOT L11
L13             ANALYZE L12 1- LC :      43 TERMS
                D 1-43

     FILE 'STNGUIDE' ENTERED AT 10:51:08 ON 02 MAR 2006

     FILE 'CAPLUS' ENTERED AT 10:58:06 ON 02 MAR 2006
L14        1074 SEA ABB=ON  L12

     FILE 'REGISTRY' ENTERED AT 10:58:14 ON 02 MAR 2006
L15           1 SEA ABB=ON  9034-40-6
                D IDE

     FILE 'CAPLUS' ENTERED AT 10:58:59 ON 02 MAR 2006
L16       16360 SEA ABB=ON  L15
L17         209 SEA ABB=ON  L16(L)ADV/RL
L18           1 SEA ABB=ON  L17 AND L14
L19          23 SEA ABB=ON  L16 AND L14
                D SCAN TI
L20         406 SEA ABB=ON  L14(L)USES/RL
                D SCAN L18
L21         499 SEA ABB=ON  RETENTION/OBI(L)FLUID#/OBI
L22         661 SEA ABB=ON  HOT/OBI(L)FL!SH?/OBI
L23        5507 SEA ABB=ON  HEADACHE#/OBI
L24        2103 SEA ABB=ON  NAUSEA/OBI
L25       11069 SEA ABB=ON  DEPRESSION/OBI(L)MENTAL/OBI
L26          40 SEA ABB=ON  (MAMMARY/OBI OR BREAST#/OBI)(L)TENDER?/OBI
L27       50049 SEA ABB=ON  CARDIOVASCULAR/OBI
L28         294 SEA ABB=ON  GYNECOMASTI?/OBI
L29          56 SEA ABB=ON  PROSTAT?/OBI(L)ENLARG?/OBI
L30           3 SEA ABB=ON  L16 AND L14 AND (L21 OR L22 OR L23 OR L24 OR L25
                OR L26 OR L27 OR L28 OR L29)
                D SCAN
L31          37 SEA ABB=ON  L20 AND (L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR
                L27 OR L28 OR L29)
L32      506947 SEA ABB=ON  ADV/RL
L33       14986 SEA ABB=ON  (SIDE/OBI OR ADVERSE/OBI)(L)(EFFECT?/OBI OR
                EVENT?/OBI)
L34          12 SEA ABB=ON  L31 AND (L32 OR L33)
                D QUE NOS
                D QUE NOS L30

     FILE 'TOXCENTER' ENTERED AT 11:20:13 ON 02 MAR 2006
L35         558 SEA ABB=ON  L12
L36        3200 SEA ABB=ON  L15
L37           7 SEA ABB=ON  L35 AND L36
                D SCAN
L38        1414 SEA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
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L39        1575 SEA ABB=ON  HOT FL!SH?
L40       20188 SEA ABB=ON  HEADACHE#
L41       36314 SEA ABB=ON  NAUSEA
L42       71854 SEA ABB=ON  DEPRESSION
L43         358 SEA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L44      213083 SEA ABB=ON  CARDIOVASCULAR
L45        1510 SEA ABB=ON  GYNECOMASTI?
L46         183 SEA ABB=ON  PROSTAT?(2A)ENLARG?
L47      808206 SEA ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR EVENT?)
L48         210 SEA ABB=ON  L35 AND (L38 OR L39 OR L40 OR L41 OR L42 OR L43 OR
                L44 OR L45 OR L46 OR L47)
L49          57 SEA ABB=ON  L35 AND (L38 OR L39 OR L40 OR L41 OR L42 OR L43 OR
                L44 OR L45 OR L46) AND L47

     FILE 'BIOSIS' ENTERED AT 11:23:24 ON 02 MAR 2006
L50        1002 SEA ABB=ON  L12
L51       13923 SEA ABB=ON  L15
L52          21 SEA ABB=ON  L50 AND L51
L53        1583 SEA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L54        1296 SEA ABB=ON  HOT FL!SH?
L55       24834 SEA ABB=ON  HEADACHE#
L56       20197 SEA ABB=ON  NAUSEA
L57      119520 SEA ABB=ON  DEPRESSION
L58         262 SEA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L59     1807338 SEA ABB=ON  CARDIOVASCULAR
L60        1659 SEA ABB=ON  GYNECOMASTI?
L61         652 SEA ABB=ON  PROSTAT?(2A)ENLARG?
L62      185953 SEA ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR EVENT?)
L63           0 SEA ABB=ON  L50 AND L51 AND (L53 OR L54 OR L55 OR L56 OR L57
                OR L58 OR L59 OR L60 OR L61 OR L62)
L64         153 SEA ABB=ON  L50 AND (L53 OR L54 OR L55 OR L56 OR L57 OR L58 OR
                L59 OR L60 OR L61 OR L62)
L65       21420 SEA ABB=ON  (LUTEINIZING OR GONADOTROPIN)(1W)RELEASING
                HORMONE#
L66           3 SEA ABB=ON  L50 AND (L51 OR L65) AND (L53 OR L54 OR L55 OR L56
                OR L57 OR L58 OR L59 OR L60 OR L61 OR L62)

     FILE 'USPATFULL' ENTERED AT 11:27:50 ON 02 MAR 2006
L67         117 SEA ABB=ON  L12
L68        1036 SEA ABB=ON  L15
L69           5 SEA ABB=ON  L67 AND L68
                D SCAN TI

     FILE 'EMBASE' ENTERED AT 11:28:44 ON 02 MAR 2006
L70        2369 SEA ABB=ON  L12
                D TRIAL 100-105
L71        2157 SEA ABB=ON  ESTRADIOL VALERATE/CT
                E GONADOTROPIN RE/CT
                E E18+ALL
                E E2+ALL
L72       20312 SEA ABB=ON  GONADORELIN/CT
L73          67 SEA ABB=ON  (L70 OR L71) AND L72
L74         197 SEA ABB=ON  L72(L)AE/CT
L75           1 SEA ABB=ON  L74 AND (L70 OR L71)
                D TRIAL
L76           0 SEA ABB=ON  L72(L)SI/CT
L77      363126 SEA ABB=ON  SIDE EFFECT/CT
L78           5 SEA ABB=ON  L73 AND L77
                D TRIAL 1-5
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     FILE 'BIOTECHNO' ENTERED AT 11:34:41 ON 02 MAR 2006
L79          357 SEA ABB=ON  L12
L80          385 SEA ABB=ON  ESTRADIOL VALERATE
L81         5768 SEA ABB=ON  L15
L82         9488 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                 LEASING(W)(FACTOR# OR  HORMONE#))
L83           48 SEA ABB=ON  (L79 OR L80) AND (L81 OR L82)
L84          279 SEA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L85          287 SEA ABB=ON  HOT FL!SH?
L86         2536 SEA ABB=ON  HEADACHE#
L87         3002 SEA ABB=ON  NAUSEA
L88         5916 SEA ABB=ON  DEPRESSION
L89           17 SEA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L90         9915 SEA ABB=ON  CARDIOVASCULAR
L91          187 SEA ABB=ON  GYNECOMASTI?
L92           43 SEA ABB=ON  PROSTAT?(2A)ENLARG?
L93        14495 SEA ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR EVENT?)
L94            5 SEA ABB=ON  L83 AND (L84 OR L85 OR L86 OR L87 OR L88 OR L89 OR
                 L90 OR L91 OR L92 OR L93)
                 D TRIAL 1-5

     FILE 'MEDLINE' ENTERED AT 11:36:51 ON 02 MAR 2006
L95          655 SEA ABB=ON  L12
                 D TRIAL 100-105
L96         4412 SEA ABB=ON  ESTRADIOL/CT(L)AA/CT
                 E GONADORELIN+ALL/CT
L97        22442 SEA ABB=ON  GONADORELIN+NT/CT
                 D PY 22442
L98          132 SEA ABB=ON  (L95 OR L96) AND L97
L99          966 SEA ABB=ON  L97(L)AE/CT
L100           7 SEA ABB=ON  L99 AND (L95 OR L96)
                 D TRIAL 1-7

     FILE 'AGRICOLA' ENTERED AT 11:40:11 ON 02 MAR 2006
L101         111 SEA ABB=ON  L12
                 D TRIAL 100-105
L102          60 SEA ABB=ON  ESTRADIOL VALERATE
L103        1744 SEA ABB=ON  L15
L104        1358 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                 LEASING(W)(FACTOR# OR  HORMONE#))
L105           7 SEA ABB=ON  (L101 OR L102) AND (L103 OR L104)
                 D TRIAL 1-7
L106          53 SEA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L107          16 SEA ABB=ON  HOT FL!SH?
L108         206 SEA ABB=ON  HEADACHE#
L109         221 SEA ABB=ON  NAUSEA
L110        3636 SEA ABB=ON  DEPRESSION
L111          36 SEA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L112        6079 SEA ABB=ON  CARDIOVASCULAR
L113           5 SEA ABB=ON  GYNECOMASTI?
L114           5 SEA ABB=ON  PROSTAT?(2A)ENLARG?
L115        7300 SEA ABB=ON  (SIDE OR ADVERSE)(2A)(EFFECT? OR EVENT?)
L116           0 SEA ABB=ON  L105 AND (L106 OR L107 OR L108 OR L109 OR L110 OR
                 L111 OR L112 OR L113 OR L114 OR L115)
                 E HUMAN/CT
                 E HUMANS/CT
                 E E3+ALL
L117        7071 SEA ABB=ON  MAN/CT
                 E WOMAN/CT
L118       10394 SEA ABB=ON  WOMEN/CT
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L119          0 SEA ABB=ON  L105 AND (L117 OR L118)

     FILE 'DRUGU' ENTERED AT 11:44:46 ON 02 MAR 2006
L120        371 SEA ABB=ON  L12
L121        816 SEA ABB=ON  ESTRADIOL VALERATE
L122          0 SEA ABB=ON  L15
L123       2266 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                LEASING(W)(FACTOR# OR  HORMONE#))
                D TRIAL 100-105
L124         14 SEA ABB=ON  (L120 OR L121) AND L123
                D TRIAL 1-14

     FILE 'STNGUIDE' ENTERED AT 11:46:33 ON 02 MAR 2006

     FILE 'DRUGU' ENTERED AT 11:52:25 ON 02 MAR 2006
L125        765 SEA ABB=ON  ESTRADIOL-VALERATE/CT
L126         12 SEA ABB=ON  (L120 OR L125) AND L123
                D TRIAL 1-12
L127       8458 SEA ABB=ON  RELEASING-FACTOR#/CT
L128          0 SEA ABB=ON  RELEASING-FACTOR *AE/CT OR RELEASING-FACTORS
                *AE/CT
L129         33 SEA ABB=ON  (L120 OR L125) AND L127
L130         10 SEA ABB=ON  (L120 OR L125) AND L127 AND L123
L131     311308 SEA ABB=ON  AE
                D TRIAL
L132          6 SEA ABB=ON  L130 AND L131
                D TRIAL 1-6
L133          0 SEA ABB=ON  ADVERSE REACTIONS/CT
L134     240306 SEA ABB=ON  ADVERSE REACTIONS/CC
L135          6 SEA ABB=ON  L130 AND (L131 OR L134)
L136       6084 SEA ABB=ON  FLUSHING/CT
                E HEADACHE/CT
L137      24956 SEA ABB=ON  HEADACHE/CT
                E FLUID RET/CT
                E NAUSEA/CT
L138      42819 SEA ABB=ON  NAUSEA/CT
                E DEPRESSION/CT
                E E3+ALL
L139      15233 SEA ABB=ON  DEPRESSION/CT
                E WEIGHT-GAIN/CT
L140       3693 SEA ABB=ON  WEIGHT-GAIN/CT
                E GYNECOMASTIA/CT
L141        606 SEA ABB=ON  GYNECOMASTIA/CT
                E PROSTATE ENL/CT
                E PROSTATE-ENL/CT
L142        676 SEA ABB=ON  PROSTATE-HYPERPLASIA/CT OR PROSTATE-HYPERTROPHY/CT

L143        582 SEA ABB=ON  (MAMMARY OR BREAST#)(2A)TENDER?
L144       1427 SEA ABB=ON  (RETENTION OR RETAIN?)(2A)FLUID#
L145      23742 SEA ABB=ON  CARDIOVASCULAR
L146          5 SEA ABB=ON  L130 AND (L136 OR L137 OR L138 OR L139 OR L140 OR
                L141 OR L142 OR L143 OR L144 OR L145)
L147          6 SEA ABB=ON  L146 OR L135

     FILE 'IPA' ENTERED AT 12:01:26 ON 02 MAR 2006
L148         71 SEA ABB=ON  L12
L149         81 SEA ABB=ON  ESTRADIOL VALERATE
L150          1 SEA ABB=ON  L15
L151        764 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                LEASING(W)(HORMONE# OR FACTOR#))
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L152          4 SEA ABB=ON  (L148 OR L149) AND (L150 OR L151)
                D TRIAL 1-4

     FILE 'SCISEARCH' ENTERED AT 12:02:51 ON 02 MAR 2006

     FILE 'IMSRESEARCH' ENTERED AT 12:03:09 ON 02 MAR 2006
L153          2 SEA ABB=ON  L12
L154         13 SEA ABB=ON  ESTRADIOL VALERATE
L155          0 SEA ABB=ON  L15
L156         74 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                LEASING(W)(HORMONE# OR FACTOR#))
L157          0 SEA ABB=ON  (L153 OR L154) AND L156

     FILE 'ADISINSIGHT' ENTERED AT 12:03:45 ON 02 MAR 2006
L158          2 SEA ABB=ON  L12
L159          9 SEA ABB=ON  ESTRADIOL VALERATE
L160          0 SEA ABB=ON  L15
L161         64 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                LEASING(W)(HORMONE# OR FACTOR#))
L162          1 SEA ABB=ON  (L158 OR L159) AND L161
                D SCAN
                D KWIC

     FILE 'WPIDS' ENTERED AT 12:04:50 ON 02 MAR 2006
L163         62 SEA ABB=ON  ESTRADIOL VALERATE
L164        678 SEA ABB=ON  GONADORELIN OR ((LUTEINIZING OR GONADOTROPIN)(1W)RE
                LEASING(W)(HORMONE# OR FACTOR#))
L165          1 SEA ABB=ON  L163 AND L164
                D TRIAL

     FILE 'STNGUIDE' ENTERED AT 12:05:32 ON 02 MAR 2006

     FILE 'REGISTRY' ENTERED AT 12:08:13 ON 02 MAR 2006
                D STAT QUE L12

     FILE 'CAPLUS' ENTERED AT 12:08:14 ON 02 MAR 2006
                D QUE NOS L18
                D QUE NOS L30
L166          3 SEA ABB=ON  L18 OR L30

     FILE 'TOXCENTER' ENTERED AT 12:08:16 ON 02 MAR 2006
                D QUE NOS L37

     FILE 'BIOSIS' ENTERED AT 12:08:17 ON 02 MAR 2006
                D QUE NOS L66

     FILE 'USPATFULL' ENTERED AT 12:08:18 ON 02 MAR 2006
                D QUE NOS L69

     FILE 'EMBASE' ENTERED AT 12:08:19 ON 02 MAR 2006
                D QUE NOS L75
                D QUE NOS L78
L167          5 SEA ABB=ON  L75 OR L78

     FILE 'BIOTECHNO' ENTERED AT 12:08:20 ON 02 MAR 2006
                D QUE NOS L94

     FILE 'AGRICOLA' ENTERED AT 12:08:23 ON 02 MAR 2006
                D QUE NOS L116
                D QUE NOS L119
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     FILE 'DRUGU' ENTERED AT 12:08:24 ON 02 MAR 2006
                D QUE NOS L135
                D QUE NOS L146
L168             6 SEA ABB=ON  L135 OR L146

     FILE 'IPA' ENTERED AT 12:08:26 ON 02 MAR 2006
                D QUE NOS L152

     FILE 'IMSRESEARCH' ENTERED AT 12:08:27 ON 02 MAR 2006
                D QUE NOS L157

     FILE 'ADISINSIGHT' ENTERED AT 12:08:28 ON 02 MAR 2006
                D QUE NOS L162

     FILE 'MEDLINE' ENTERED AT 12:08:29 ON 02 MAR 2006
                D QUE NOS L100

     FILE 'STNGUIDE' ENTERED AT 12:08:36 ON 02 MAR 2006

     FILE 'CAPLUS, USPATFULL, MEDLINE, DRUGU, BIOTECHNO, IPA, BIOSIS, EMBASE,
     TOXCENTER, ADISINSIGHT' ENTERED AT 12:10:30 ON 02 MAR 2006
L169            41 DUP REM L166 L69 L100 L168 L94 L152 L66 L167 L37...   (5 DUPLIC
                      ANSWERS '1-3' FROM FILE CAPLUS
                      ANSWERS '4-7' FROM FILE USPATFULL
                      ANSWERS '8-14' FROM FILE MEDLINE
                      ANSWERS '15-19' FROM FILE DRUGU
                      ANSWERS '20-24' FROM FILE BIOTECHNO
                      ANSWERS '25-27' FROM FILE IPA
                      ANSWERS '28-30' FROM FILE BIOSIS
                      ANSWERS '31-35' FROM FILE EMBASE
                      ANSWERS '36-40' FROM FILE TOXCENTER
                      ANSWER '41' FROM FILE ADISINSIGHT
                D IBIB ED ABS HITSTR 1-7
                D IALL 8-41

     FILE 'CAPLUS' ENTERED AT 12:11:23 ON 02 MAR 2006
                D QUE NOS L34
L170            10 SEA ABB=ON  L34 NOT L166
                D IBIB ED ABS HITSTR L170 1-10

     FILE 'HOME' ENTERED AT 12:11:37 ON 02 MAR 2006
                D SAVED
                D STAT QUE L12

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